Loss of Interleukin 1 Receptor Antagonist Enhances Susceptibility to Ebola Virus Infection

Lindsay Hill-Batorski,1 Peter Halfmann,1 Andrea Marzi,2 Tiago J. S. Lopes,1,3 Gabriele Neumann,1 Heinz Feldmann,2 and Yoshihiro Kawaoka1,3,4

1Department of Pathobiological Sciences, School of Veterinary Medicine, Influenza Research Institute, University of Wisconsin–Madison; 2Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana; 3Division of Virology, Department of Microbiology and Immunology, International Research Center for Infectious Diseases, Institute of Medical Science, University of Tokyo, and 4ERATO Infection-Induced Host Responses Project, Japan Science and Technology Agency, Saitama, Japan

The current outbreak of Ebola virus (EBOV) infection in West Africa is unprecedented, with nearly 26,000 confirmed cases and >10,000 deaths. Comprehensive data on the pathogenesis of EBOV infection are lacking; however, recent studies suggested that fatal EBOV infections are characterized by dysregulation of the innate immune response and a subsequent cytokine storm. Specifically, several studies suggested that hypersecretion of interleukin 1 receptor antagonist (IL-1Ra) correlates with lethal EBOV infections. To examine the significance of IL-1Ra in EBOV infections, we infected mice that lack the gene encoding IL-1Ra, Il1rn (IL-1RN-KO), and mice with wild-type Il1rn (IL-1RN-WT) with a mouse-adapted EBOV (MA-EBOV). Infected IL-1RN-KO mice lost more weight and had a lower survival rate than IL-1RN-WT mice infected with MA-EBOV. In addition, IL-1RN-KO mice infected with wild-type EBOV, which does not cause lethal infection in adult immunocompetent mice, such as C57BL/6 mice, experienced greater weight loss than IL-1RN-WT mice infected with wild-type EBOV. Further studies revealed that the levels of 6 cytokines in spleens—IL-1α, IL-1β, interleukin 12p40, interleukin 17, granulocyte colony-stimulating factor, and regulated on activation, normal T-cell expressed and secreted—were significantly different between IL-1RN-KO mice and IL-1RN-WT mice infected with MA-EBOV. Collectively, our data suggest that IL-1Ra may have a protective effect upon EBOV infection, likely by damping an overactive proinflammatory immune response.

Keywords. Ebola virus; interleukin 1 receptor antagonist; Il1rn; IL-1Ra.

The virus family Filoviridae consists of 3 distinct genera, Cuevavirus, Marburgvirus, and Ebolavirus. Members of the Filoviridae are enveloped viruses and contain a nonsegmented, negative-strand RNA genome. Ebola virus (EBOV) is one of the causative agents of Ebola hemorrhagic fever, a disease characterized by coagulation disorder, multiple organ system failure, and often death [1–3]. The first recorded outbreak of EBOV infection occurred in Zaire (now the Democratic Republic of the Congo) in 1976. With 318 cases and a case-fatality rate of 88%, it was the deadliest EBOV outbreak on record [4]. Since then, EBOV has reemerged intermittently, mainly in remote areas of central Africa. A new outbreak started in early 2014 and spread to urbanized areas in West Africa, which has resulted in >25,000 cases and 10,602 deaths as of 10 April 2015 [4]. The unprecedented scale of this outbreak has highlighted the need for a more thorough understanding of EBOV pathogenesis.

Owing to the sporadic nature of EBOV outbreaks and the biosafety concerns associated with sample collection, comprehensive data on the pathogenesis of human EBOV infections are lacking. However, limited data compiled from infected people and nonhuman primates (NHPs) suggested that severe dysregulation of the innate immune response, resulting in a cytokine storm, is associated with severe disease and fatal outcome [1, 5–8]. In particular, 3 independent studies found that hypersecretion of interleukin 1 receptor antagonist (IL-1Ra) was associated with fatal human cases of EBOV infection [5, 8, 9]. This trend is also appreciated in animal models, specifically NHPs, which had...
robustly elevated levels of IL-1Ra starting 4–5 days after infection with EBOV [10], and mice, in which transcript levels of IL-1Ra in the spleens following mouse-adapted EBOV (MA-EBOV) infection correlated with viral titers and lethality [11]. IL-1Ra competes with IL-1 for binding to the IL-1 receptor, blocking IL-1–induced proinflammatory signaling, and may, through this mechanism, affect viral pathogenicity. The importance of IL-1Ra as an antiinflammatory mediator is further supported by data involving patients with mutations in IL1RN, in whom loss of IL-1Ra results in life-threatening systemic inflammation [12, 13], as well as an increased risk of cancer and coronary disease due to chronic inflammation [14, 15]. To gain further insight into the role of IL-1Ra during EBOV pathogenesis, Il1rn wild-type (IL-1RN-WT) and knockout (IL-1RN-KO) mice were infected with wild-type EBOV (WT-EBOV) and MA-EBOV. IL-1RN-KO mice were more susceptible to infection with both viruses, compared with IL-1RN-WT mice, suggesting that IL-1Ra has a protective effect during EBOV infection.

MATERIALS AND METHODS

Animal Ethics and Safety Statements

Research was approved and conducted in compliance with the guidelines of Institutional Animal Care and Use Committee (IACUC), Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases (Hamilton, Montana). The facility where this research was conducted is fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International and has an approved Office of Laboratory Animal Welfare assurance number (A4149-01). All procedures were conducted by trained personnel under the supervision of veterinarians, and all invasive clinical procedures were performed while animals were anesthetized. Early end point criteria, as specified by the IACUC-approved scoring parameters, were used to determine when animals should be humanely euthanized. Ebolaviruses are classified as biosafety level 4 (BSL-4) pathogens, and all work with these viruses was approved by the institutional biosafety committee under BSL4 conditions.

Viruses

WT-EBOV and MA-EBOV (strain Mayinga) were generated and titered as previously described [16–19]. All research conducted with live EBOV was performed in the BSL-4 laboratory at Rocky Mountain Laboratories.

Mouse Experiments

Female IL-1RN-WT C57BL/6J mice and IL-1RN-KO mice (C57BL/6J background) aged 6–8 weeks were purchased from Jackson Laboratories. All mice were housed in microisolator cages and allowed to acclimate for 7 days prior to the experiment.

For inoculation, 12 mice per group were anesthetized with isoflurane and infected intraperitoneally with the indicated focus-forming units (FFU) of WT-EBOV or MA-EBOV. The animals were then monitored for clinical signs and weighed daily. To measure virus titers and cytokine levels, animals were infected as described above. We then euthanized 3–4 animals per group on days 2, 4, and 6 after infection and collected the spleens for virus titration and cytokine analyses.

Cytokine Secretion Analyses

Spleens were homogenized using a TissueLyser II (Qiagen) in sterile culture medium. After pelleting cell debris, spleen homogenates were gamma-irradiated with 10 MRads (according to approved standard operating protocol) before removal from the BSL-4 laboratory. Spleen homogenates were then evaluated for the presence of cytokines by using a Bio-Plex Pro Mouse Cytokine 23-Plex Panel Assay (Bio-Rad, Hercules, California) in a Bio-Plex 200 System, following the instructions provided by the manufacturer. The Mouse Cytokine 23-Plex Panel consists of the following analytes: IL-1α, IL-1β, interleukin 2 (IL-2), interleukin 3 (IL-3), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 9 (IL-9), interleukin 10 (IL-10), interleukin 12p40 (IL-12p40), IL-12p70, interleukin 13 (IL-13), interleukin 17 (IL-17), chemokine C-X-C motif ligand 1 (KC), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, regulated on activation, normal T-cell expressed and secreted (RANTES), tumor necrosis factor α (TNF-α), eotaxin, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage CSF (GM-CSF), and interferon γ (IFN-γ).

Statistical Analysis

The statistical tests were performed by using GraphPad Prism v6.0. To compare the survival rates of infected animals, log-rank (Mantel–Cox) tests were performed. To assess the weight loss of mice, we performed multiple t tests comparing the average weights of infected IL-1RN-WT and IL-1RN-KO mice at each time point; the P values were adjusted for multiple comparisons, using the Holm–Sidak method. For the comparison of cytokine levels of infected animals, we performed 2-way analysis of variance (ANOVA) taking into account the genetic background of the animals (ie, IL-1RN-WT or IL-1RN-KO) and the different time points. The averages of different groups at each time point were compared and the P values adjusted using the Holm–Sidak method. Finally, to compare the cytokine levels of infected and noninfected animals at different time points, we used 1-way ANOVA, followed by the Dunnett test. In all cases, the family wise significance level was set at .05, and P values were considered significant if they were <.05.

RESULTS AND DISCUSSION

The host factors affecting EBOV pathogenicity in humans are largely unknown. Several studies suggested that the secretion
of high levels of the antiinflammatory marker IL-1Ra is associated with fatal outcome of EBOV infections in humans [5, 8, 9] or with high viral titers and lethality in mice infected with MA-EBOV [11].

To gain further insight into the role of IL-1Ra in EBOV pathogenesis, we inoculated IL-1RN-WT and IL-1RN-KO mice intraperitoneally with 1.0 FFU or 0.1 FFU of MA-EBOV [16, 17, 20]. These viral doses were not uniformly lethal in WT mice, allowing detection of potential differences in lethality between the 2 groups. Mice were observed over 10 days for weight loss and signs of illness. Both groups of mice exhibited similar clinical signs during the course of infection, including ruffled fur, hunched posture, and lethargy. However, IL-1RN-KO mice infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

To compare virus titers in IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV, we inoculated mice (3–4 per group) with 0.1 FFU of MA-EBOV and euthanized animals on days 2, 4, and 6 after infection. Spleens were collected, homogenized, and assessed for virus titers by performing plaque assays in Vero cells. Spleens were chosen as sampling sites primarily because the spleen is a major target organ of EBOV [21, 22] and infected with MA-EBOV lost weight more rapidly that infected IL-1RN-WT mice (Figure 1A and 1B). More importantly, all infected IL-1RN-KO mice died on days 6–8 after infection, while wild-type mice had survival rates of 33% and 45%, respectively (Figure 1D and 1E). These findings suggest that the lack of IL-1Ra increased the susceptibility of mice to EBOV infection.

Figure 1. Survival and weight loss among wild-type Il1rn (IL-1RN-WT) mice and Il1rn knockout (IL-1RN-KO) mice infected with mouse-adapted Ebola virus (MA-EBOV) and WT EBOV (WT-EBOV). IL-1RN-WT and IL-1RN-KO mice were inoculated intraperitoneally with 1 focus-forming unit (FFU; A and D) or 0.1 FFU (B and E) of MA-EBOV or with 1000 FFU of WT-EBOV (C and F). Weight loss (A–C) and survival (D–F) were monitored for 10 days. Weight loss data are presented as means ± SD. *P ≤ .05 for the difference between IL-1RN-WT and IL-1RN-KO mice.
because previous microarray analysis of spleen samples identified increased levels of IL-1Ra transcripts associated with EBOV lethality in mice. On day 2 after infection, virus titers were below the level of detection in all spleen samples (Figure 2), whereas on day 4 after infection, infected IL-1RN-WT and IL-1RN-KO mice showed comparable virus titers in the spleen (Figure 2). In contrast, only 2 infected IL-1RN-WT mice had detectable virus titers in their spleens on day 6 after infection. The remaining 2 infected IL-1RN-WT mice exhibited symptoms of MA-EBOV infection, suggesting that they had been infected, but no virus was detected in the spleen of these animals on day 6 after infection. Hence, IL-1RN-KO mice may be impaired in their ability to clear MA-EBOV infection, consistent with higher weight loss and mortality rates in these animals (Figure 1).

Since the lack of IL-1Ra seemingly increased the susceptibility of mice to infection with MA-EBOV, we next examined whether IL-1RN-KO mice would be susceptible to infection with WT-EBOV, which does not cause any clinical symptoms in immunocompetent adult mice [19, 23]. Interestingly, all IL-1RN-WT and IL-1RN-KO mice infected with 1000 FFU of WT-EBOV (a dose shown previously to result in 100% lethality in immunodeficient mice [24]) survived the infection (Figure 1F). However, IL-1RN-KO mice exhibited slight but statistically significant weight loss, in contrast to IL-1RN-WT mice (Figure 1C). These data again demonstrate that mice lacking IL-1Ra may be more susceptible to EBOV infection than wild-type mice.

The finding that IL-1RN-KO mice are more susceptible to EBOV infection was in contrast to the elevated levels of IL-1Ra that have been shown to correlate with increased lethality in humans and mice infected with EBOV and MA-EBOV, respectively [5, 8, 9, 11]. Elevated levels of IL-1Ra have been described in patients with several infectious diseases [25–29], but the role and potential benefits or detriments of IL-1Ra are unclear. For example, some studies have shown that high levels of IL-1Ra correlate with higher survival rate after septic shock [30, 31], while others have found that high IL-1Ra levels are indicative of fatal septicemia [32]. IL-1RN-KO mice are more sensitive to bacterial lipopolysaccharide-induced lethality than WT mice [33] yet are more resistant to pneumococcal bacterial challenge [34]. During infection, a delicate balance exists between the beneficial effects of pathogen clearance and the detrimental effects of an overactive immune response. Hypersecretion of IL-1Ra, together with other antiinflammatory cytokines whose levels have been shown to increase during EBOV infection (eg, IL-10), may represent a last-ditch effort to control an exaggerated immune response, while complete loss of IL-1Ra may render animals less capable of controlling the rapid production of inflammatory mediators typically detected during EBOV infection.

Based on the role of IL-1Ra in innate immunity, we speculated that IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV may differ in the expression levels of cytokines. We, therefore, analyzed the spleens of MA-EBOV–infected IL-1RN-WT and IL-1RN-KO mice collected on days 2, 4, and 6 after infection for the levels of 23 different murine cytokines. The levels of 7 cytokines (IL-3, IL-4, IL-5, IL-9, IL-10, IFN-γ, and TNF-α) were remarkably similar between the 2 groups of mice (data not shown). Consistent with previous reports [1, 5–8], the levels of 9 cytokines (IL-1α, IL-6, IL-12p40, IL-12p70, G-CSF, KC [murine IL-8], MCP-1, MIP-1α, and MIP-1β) were significantly increased in infected IL-1RN-WT and IL-1RN-KO mice, compared with noninfected animals, at least at 1 time point (Figure 3). The levels of 4 cytokines (IL-1β, IL-2, eotaxin, and GM-CSF) were significantly lower in infected IL-1RN-WT mice, compared with noninfected control mice (Figure 3). Although the levels of these 4 cytokines were also lower in infected IL-1RN-KO mice, compared with noninfected controls, the differences were not statistically significant.

For 6 cytokines—IL-1α, IL-1β, IL-12p70, IL-17, G-CSF, and RANTES—expression levels differed between IL-1RN-WT and IL-1RN-KO mice infected with MA-EBOV (Figure 3). In spleens from infected IL-1RN-KO mice, significantly lower levels of IL-1α and IL-12p70 were expressed on day 4 after infection, compared with spleens from infected IL-1RN-WT mice. Conversely, IL-1RN-KO mice expressed significantly higher levels of 4 cytokines, including IL-1β on days 4 and 6 after infection, IL-17 on day 2 after infection, G-CSF on day 6 after infection, and RANTES on day 2 after infection, compared with infected wild-type mice. Interestingly, these 4 cytokines are known to specifically modulate neutrophil migration and function. Recruitment of neutrophils in response to several pathogens requires the upregulation and release of IL-1β [35, 36].

Figure 2. Viral titers in the spleens among wild-type Il1rn (IL-1RN-WT) mice and Il1rn knockout (IL-1RN-KO) mice infected with mouse-adapted Ebola virus (MA-EBOV). IL-1RN-WT and IL-1RN-KO mice were inoculated intraperitoneally with 0.1 focus-forming units (FFU) of MA-EBOV and euthanized on days 2, 4, or 6 after infection. Spleens were collected, homogenized, and assayed for virus titration. Virus titers, shown as FFU, were calculated per gram of spleen tissue and are presented as means ± SD. Abbreviation: ND, virus was not detected.
Figure 3. Cytokine analysis of spleen samples derived from wild-type Il1rn (IL-1RN-WT) mice and Il1rn knockout (IL-1RN-KO) mice infected with mouse-adapted Ebola virus (MA-EBOV). IL-1RN-KO and IL-1RN-WT mice were inoculated intraperitoneally with 0.1 focus-forming units (FFU) of MA-EBOV and euthanized on days 2, 4, or 6 after infection. Spleens were collected and homogenized, and cytokine analysis was performed. Cytokine concentrations are shown as picograms per gram of spleen tissue. Samples obtained from IL-1RN-WT mice are represented as circles, with the mean denoted by the solid bar, while those obtained from IL-1RN-KO mice are depicted by an X, with the mean denoted by the dotted bar. For the 6 cytokines whose expression levels differed between infected IL-1RN-KO and IL-1RN-WT mice, statistically significant differences (P < .05) are indicated by boxes. Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-2, interleukin 2; IL-6, interleukin 6; IL-12, interleukin 12; IL-13, interleukin 13; IL-17, interleukin 17; KC, chemokine C-X-C motif ligand 1; MCP-1, monocyte chemoattractant protein 1; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T-cell expressed and secreted.
Con several leukocytes, including neutrophils [41]. Hence, higher infection [39, 40]. Finally, RANTES regulates chemotaxis in neutrophil survival, number, and recruitment at the site of infection. Previous studies indicate that a marked rise in blood neutrophil count is one of the earliest abnormalities documented during EBOV infection in humans and NHPs and is a prominent feature in fatal cases [42–45]. Since neutrophils are particularly cytotoxic, owing to their potent oxidative antimicrobial properties, increased numbers or prolonged survival of neutrophils at the site of infection can contribute to tissue injury [46–48], perhaps contributing to the increased susceptibility of IL-1RN KO mice to MA-EBOV infection. Further experiments with IL-1RN KO mice will be necessary to assess the role of IL-1Ra in neutrophil recruitment and activation during EBOV infection in more detail.

In summary, IL-1RN KO mice are more susceptible to increased disease severity and death during EBOV infection than IL-1RN WT mice. This difference in lethality correlated with potential differences in viral clearance and altered expression levels of cytokines known to modulate neutrophil action. Together, these data suggest that IL-1Ra may contribute to the protection of the host during EBOV infection.

Notes

Financial support. This work was supported by the National Institutes of Health (NIH; project5 U19 AI106772-02) and by the intramural research program of the National Institute of Allergy and Infectious Diseases, NIH.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


