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RESEARCH ARTICLE

Infectious Disease

Type I IFN Signaling Protects Mice from Lethal SARS-CoV-2 Neuroinvasion

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ABSTRACT

Multiple organ damage is common in patients with severe COVID-19, even though the underlying pathogenic mechanisms remain unclear. Acute viral infection typically activates type I IFN (IFN-I) signaling. The antiviral role of IFN-I is well characterized in vitro. However, our understanding of how IFN-I regulates host immune response to SARS-CoV-2 infection in vivo is incomplete. Using a human ACE2-transgenic mouse model, we show in the present study that IFN-I receptor signaling is essential for protection against the acute lethality of SARS-CoV-2 in mice. Interestingly, although IFN-I signaling limits viral replication in the lung, the primary infection site, it is dispensable for efficient viral clearance at the adaptive phase of SARS-CoV-2 infection. Conversely, we found that in the absence of IFN-I receptor signaling, the extreme animal lethality is consistent with heightened infectious virus and prominent pathological manifestations in the brain. Taken together, our results in this study demonstrate that IFN-I receptor signaling is required for restricting virus neuroinvasion, thereby mitigating COVID-19 severity. *ImmunoHorizons*, 2022, 6: 716–721.

INTRODUCTION

The pandemic coronavirus SARS-CoV-2 warrants critical investigation of fundamental pathogenic mechanisms. Type I IFNs (IFN-Is), particularly IFN-α/β, are often recognized as key innate cytokines for limiting virus replication and promoting adaptive immune response during acute infection (1–3). The inhibitory effect of IFN-Is on SARS-CoV-2 replication is well characterized in vitro (1, 4–8); however, our understanding of their role in vivo during COVID-19 pathogenesis remains incomplete.

It has been shown in African green monkeys that SARS-CoV-2 induces localized and sustained upregulation of IFN transcriptomic pathways in the lung as compared with the quickly resolved systemic responses (9). In a mouse model based on adeno-associated virus–mediated expression of human angiotensin I–converting enzyme-2 (hACE2), it has been suggested that IFN-I receptor signaling does not control SARS-CoV-2 replication, but rather drives pathological responses (10). In line with this, IFN-I has been suggested to be involved in COVID-19 pathology in multiple other studies (11–13).

To determine how IFN-I signaling regulates the immune balance between viral control and pathological response during SARS-CoV-2 infection in vivo, we have developed an hACE2-transgenic IFN-I receptor gene-deficient (hACE2*Ifnar1*$^{-/-}$) mouse model via cross breeding *Ifnar1*$^{-/-}$ mice with the K18-hACE2 strain. Using this human ACE2-transgenic mouse model, we show that IFN-I receptor signaling is essential for protection against COVID-19 lethality. Interestingly, hACE2*Ifnar1*$^{-/-}$ mice

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Abbreviations used in this article: BALF, bronchoalveolar lavage fluid; BBB, blood–brain barrier; DC, dendritic cell; dpi, days postinfection; hACE2, human angiotensin I–converting enzyme-2; hACE2*Ifnar1*$^{-/-}$, hACE2-transgenic IFN-I receptor gene-deficient; IFN-I, type I IFN; i.n., intranasal(ly); WT, wild-type; UTMB, University of Texas Medical Branch.

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are competent in T cell recruitment and viral control in the lung. In contrast, we found that the hypersusceptibility of hACE2*Ifnar1*$^{-/-}$ mice is associated with their heightened viral burden and pathological manifestation in the brain. Taken together, our data in this study demonstrate that IFN-I signaling is required for limiting virus neuroinvasion and acute animal lethality after respiratory SARS-CoV-2 infection.

MATERIALS AND METHODS

Murine model of SARS-CoV-2 infection

Specific pathogen-free C57BL/6 wild-type (WT), *Ifnar1*$^{-/-}$, and K18-hACE2 (14) mice were purchased from The Jackson Laboratory (Bar Harbor, ME) and bred at the University of Texas Medical Branch (UTMB) following Institutional Animal Care and Use Committee guidelines. hACE2*Ifnar1*$^{-/-}$ mice were generated by crossing *Ifnar1*$^{-/-}$ mice with the K18-hACE2 strain. Research conducted in this study was reviewed and approved by UTMB Institutional Biosafety Committee, and all animal experiments were carried out in accordance with UTMB Assurance of Compliance with U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals, which is on file with the Office of Protection from Research Risks (National Institutes of Health).

SARS-CoV-2 strain USA-WA1/2020 was provided by the World Reference Center for Emerging Viruses and Arboviruses and originally isolated by the Centers for Disease Control and Prevention. COVID-19 was induced through intranasal (i.n.) infection of anesthetized, sex- and age-matched adult mice with USA-WA1/2020 at 300 or 1500 PFU/mouse in 50 μl of sterile PBS. Titers of virus stocks and viral levels in the organs of infected mice were determined by 50% tissue culture-infective dose assays on Vero E6 cell monolayers. Animal body weight and mortality were monitored twice daily until day 20 after viral infection.

Bronchoalveolar lavage cell analysis

Bronchoalveolar lavage fluid (BALF) samples were collected by making an incision in the trachea and lavaging the lung twice with 0.8 ml of PBS (pH 7.4). For flow cytometry analysis, BALF cells were incubated with 2.4G2 mAb against FcγRII/III and stained with allophycocyanin-conjugated anti-CD11c (BioLegend), BV510-conjugated anti-CD11b (BioLegend), PE-Cy7–conjugated anti-Ly6G (clone 1A8, BioLegend), PerCP-Cy5.5–conjugated anti-Ly6C (BioLegend), BV421-conjugated anti–Siglec-F (BioLegend), and PE-conjugated anti-TCR$_\beta$ mAbs. The stained cells were fixed for 24 h in 2% paraformaldehyde before analyzing on a MACSQuant Analyzer 10 and using FlowJo software for analysis.

Histology analysis

Mice were euthanized 7 d after viral infection, and the lungs and brains were collected and fixed in 10% neutral buffered formalin solution for 7 d before histological analyses. Paraffin-embedded tissues were sectioned to a thickness of 5 μm and stained with H&E using standard methods. Whole-mount H&E-stained lung tissues were scanned using a Leica Aperio LV1 scanner and software. Lung tissues were semiquantitatively assessed at low power (×40) for the proportion of parenchyma with alveoli containing intraluminal material in the background of interstitial expansion and inflammation. Each lung was scored by the relative amount of abnormal tissue as follows: 0, normal, 1, 1–25%; 2, 26–50%; 3, 51–75%; 4, >76% (15). Digital images were generated using Leica Biosystems Aperio ImageScope 12.

Statistical analysis

Significant differences between experimental groups were determined using an ANOVA analysis followed by a two-tailed Student *t* test (to compare two samples) in GraphPad Prism 9 (GraphPad Software, La Jolla, CA). Survival analyses were performed using the log-rank test. For all analyses, a p value <0.05 was considered to be significant.

RESULTS

IFN-I receptor signaling attenuates COVID-19 lethality

To determine the role of IFN-I signaling in vivo, C57BL/6 WT, *Ifnar1*$^{-/-}$, K18-hACE2 (hACE2_WT), and hACE2*Ifnar1*$^{-/-}$ mice were i.n. challenged with SARS-CoV-2 to induce animal morbidity and mortality. In the absence of human ACE2 expression, C57BL/6WT and *Ifnar1*$^{-/-}$ mice did not exhibit any morbidity after 1500 PFU/mouse of viral infection (Fig. 1A). Conversely, this viral inoculum resulted in ≥25% weight loss and ∼50% (LD_{50}) mortality in hACE2_WT mice (Fig. 1B). At the same time, hACE2*Ifnar1*$^{-/-}$ mice appeared to have delayed weight loss compared with hACE2_WT controls (Fig. 1A); nonetheless, their symptoms worsened and all hACE2*Ifnar1*$^{-/-}$

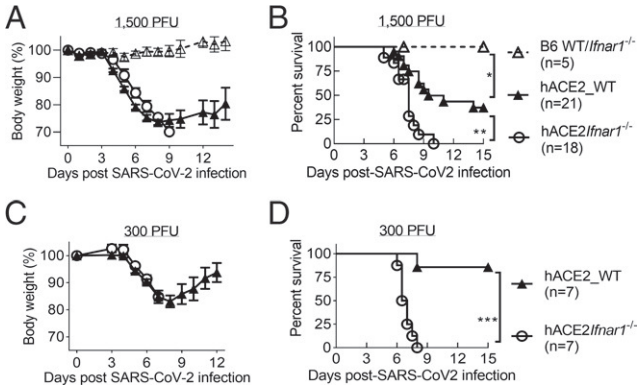

FIGURE 1. *Ifnar1* deficiency renders K18-hACE2 mice hypersusceptible to SARS-CoV-2 infection.

(**A**–**D**) Body weights (mean ± SE) and survival of C57BL/6 WT or *Ifnar1*$^{-/-}$ mice and hACE2-transgenic WT (hACE2_WT) and *Ifnar1*$^{-/-}$ (hACE2*Ifnar1*$^{-/-}$) mice after i.n. infection with (A and B) 1500 and (C and D) 300 PFU/mouse of SARS-CoV-2 virus. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, log-rank test. Data shown are representative of at least two independent experiments.

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animals succumbed to COVID-19 within 10 d (Fig. 1B). After a lower dose ($0.2LD_{50}$) of SARS-CoV-2 infection, hACE2_WT mice exhibited reduced weight loss (<20%) and mortality as compared with the LD_{50} infection (Fig. 1C, 1D). In contrast, none of hACE2*Ifnar1*$^{-/-}$ mice was able to recover from this low dose of viral infection, not even an apparent delay in time to death (Fig. 1D). Taken together, these data indicate that IFN-I receptor signaling is essential for host resistance to COVD-19 lethality.

IFN-I receptor signaling is not essential for viral control in the lung

We next assessed whether IFN-I signaling confers protection by promoting acute antiviral immunity in the lung. It has been shown that IFN-I signaling increases monocytes but inhibits neutrophil recruitment during influenza virus infection (4, 16). Interestingly, after SARS-CoV-2 infection, FACS analysis of BALF cells revealed limited neutrophil (CD11b$^+$Ly6G$^+$) accumulation even in the absence of IFN-I signaling (Fig. 2). Nonetheless, compared with hACE2_WT controls, hACE2*Ifnar1*$^{-/-}$ mice exhibited decreased infiltrating monocytes (CD11b$^+$Ly6C$^+$ and dendritic cells (DCs) (CD11c$^+$Siglec-F$^-$) in the airway (Fig. 2B). The number of alveolar macrophages (CD11c$^+$ Siglec-F$^+$) was actually increased in hACE2*Ifnar1*$^{-/-}$ mice as compared with hACE2_WT controls at 7 d postinfection (dpi). Of note, hACE2*Ifnar1*$^{-/-}$ mice exhibited similar airway TCR$_\beta^+$ T cell infiltration as hACE2_WT controls, despite their decreased NK1.1$^+$ cells at 7 dpi (Fig. 2B, 2C). These findings suggest that IFN-I signaling promotes monocyte infiltration but is dispensable for αβ T cell recruitment into the airway during SARS-CoV-2 infection.

To determine whether IFN-I signaling is essential for controlling viral infection in the lung, we examined viral burdens at days 4 and 7 after SARS-CoV-2 infection. Although there were ~2-fold increased viral titers in hACE2*Ifnar1*$^{-/-}$ lungs compared with hACE2_WT controls at 4 dpi (Fig. 3A), both groups of mice exhibited efficient lung viral clearance by 7 dpi (Fig. 3B). These results suggest that although IFN-I signaling contributes to initial inhibition of viral replication, it is not essential for lung viral control at the adaptive phase of SARS-CoV-2 infection.

IFN-I receptor signaling inhibits SARS-CoV-2 neuroinvasion

We wanted to examine whether IFN-I signaling is essential for preventing SARS-CoV-2 systemic invasion, secondary to viral replication in the lung. Therefore, we evaluated the viral load in other organs after i.n. infection with 1500 PFU/mouse of SARS-CoV-2. Infectious virus was barely detectable in the spleen and kidney of both hACE2_WT and hACE2*Ifnar1*$^{-/-}$ mice at 7 dpi (Fig. 3C, 3D), indicating that IFN-I signaling is dispensable for preventing viral replication in these tissues.

SARS-CoV-2 has demonstrated neuroinvasive properties in human patients and animal models, even though the underlying mechanism remains unclear (17–23). In agreement with

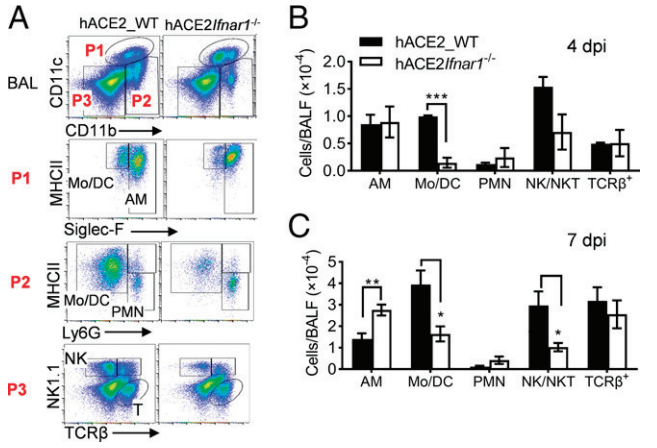

FIGURE 2. ***Ifnar1*** **deficiency does not affect airway T cell recruitment in response to SARS-CoV-2 infection.**

(**A**) Flow cytometry analysis of BALF immune cells and (**B** and **C**) the numbers of alveolar macrophages (AMs), monocytes/DCs (Mos/DCs), polymorphonuclear neutrophils (PMNs), and NK1.1$^+$ and TCR$_\beta^+$ T cells in hACE2_WT and hACE2*Ifnar1*$^{-/-}$ airways at days 4 and 7 postinfection with 1500 PFU/mouse of SARS-CoV-2 virus. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, *t* test. Data shown are representative of two independent experiments.

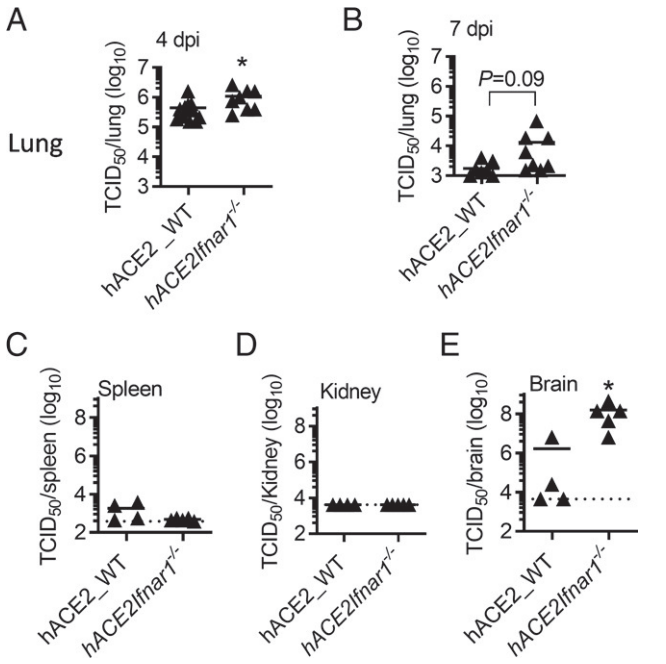

FIGURE 3. ***Ifnar1*** **deficiency is associated with severe neuroinvasion after SARS-CoV-2 infection.**

(**A** and **B**) Lung viral titers at 4 (A) and 7 (B) dpi. (**C**–**E**) Viral titers in the spleen (C), kidney (D), and brain (E) at day 7 in hACE2_WT and hACE2*Ifnar1*$^{-/-}$ mice after 1500 PFU/mouse of SARS-CoV-2 virus infection. *$p < 0.05$, *t* test. Data shown are representative of two independent experiments.

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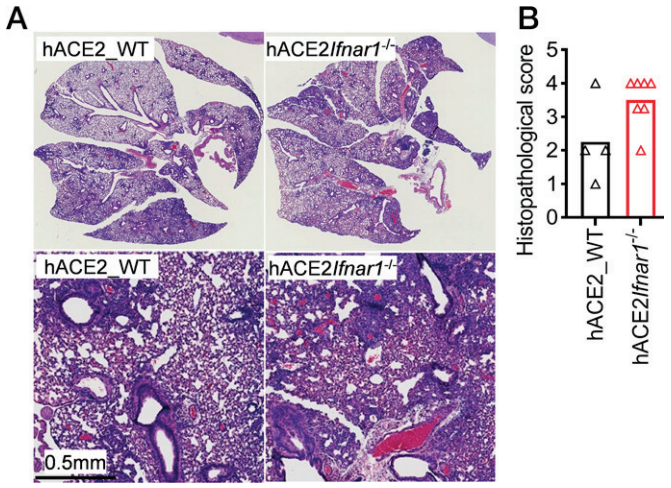

FIGURE 4. SARS-CoV-2 infection induces pathological changes in the lung.

(**A**) Lung histopathology (H&E) and (**B**) histopathologic scores (each symbol represents one mouse) of hACE2_WT (n = 4) and hACE2*Ifnar1*$^{-/-}$ mice (n = 7) at day 7 after 300 PFU/mouse of SARS-CoV-2 infection.

that, we detected infectious virus in the brains at day 7 after 1500 PFU/mouse of SARS-CoV-2 infection (Fig. 3E). Interestingly, the rate of neuroinvasion in hACE2_WT and hACE2*Ifnar1*$^{-/-}$ mice was correlated with their differential mortality after this high dose of infection. Furthermore, the viral load in the brains of hACE2*Ifnar1*$^{-/-}$ mice was significantly higher than that in hACE2_WT controls (Fig. 3E), indicating a more prominent viral neuroinvasion and replication in the absence of IFN-I signaling. Taken together, our data highlight that IFN-I has specific neuroprotective functions that inhibit SARS-CoV-2 neuroinvasion.

IFN-I receptor signaling attenuates SARS-CoV-2–induced brain pathology

It has been shown that IFN-I signaling attenuates inflammatory lung damage and thereby improves host resistance to influenza virus infection (1, 4). Thus, we investigated whether IFN-I signaling confers similar protection against lung pathology during SARS-CoV-2 infection. Both hACE2_WT and hACE2*Ifnar1*$^{-/-}$ mice exhibited pathological features in the lungs at day 7 after a low dose ($0.2LD_{50}$) of SARS-CoV-2 infection (Fig. 4A). Although hACE2*Ifnar1*$^{-/-}$ mice tended to have aggravated lung injury, their histopathological scores were not significantly different from hACE2_WT controls (Fig. 4B). Thus, lung tissue damage does not fully account for the acute death of hACE2*Ifnar1*$^{-/-}$ mice after this low dose of SARS-CoV-2 infection.

Considering the extensive viral replication in the brains of hACE2*Ifnar1*$^{-/-}$ mice, we then investigated whether IFN-I signaling prevents SARS-CoV-2 neuroinvasion and therefore direct damage to the CNS. Indeed, compared with hACE2_WT controls, hACE2*Ifnar1*$^{-/-}$ mice exhibited more prominent histopathological manifestations in the brains, particularly neuropil vacuolation and multivacuolar structures across brain cortex, hippocampus, and striatum (Fig. 5). Thus, viral neuroinvasion-associated brain damage is likely the cause of acute lethality of a low dose of SARS-CoV-2 in hACE2*Ifnar1*$^{-/-}$ mice.

DISCUSSION

In the current study, we have revealed a critical role of IFN-I signaling in preventing SARS-CoV-2 neuroinvasion and brain damage. IFN-I and IFN-stimulated genes have been identified in the regulation of blood–brain barrier (BBB) permeability and the prevention of viral neuroinvasion in infectious mouse models of West Nile virus, yellow fever virus, and rabies virus (24–26). During these neurotropic viral infections, IFN-I signaling improves the antiviral response in the peripheral organs and thereby restricts viral neuroinvasion. Accordingly, in the absence of an intact IFN-I signaling pathway, an elevated level of viremia in the periphery promotes virus transmission into the brain.

In this study, we show that during SARS-CoV-2 respiratory infection, IFN-I signaling is dispensable for viral control in the

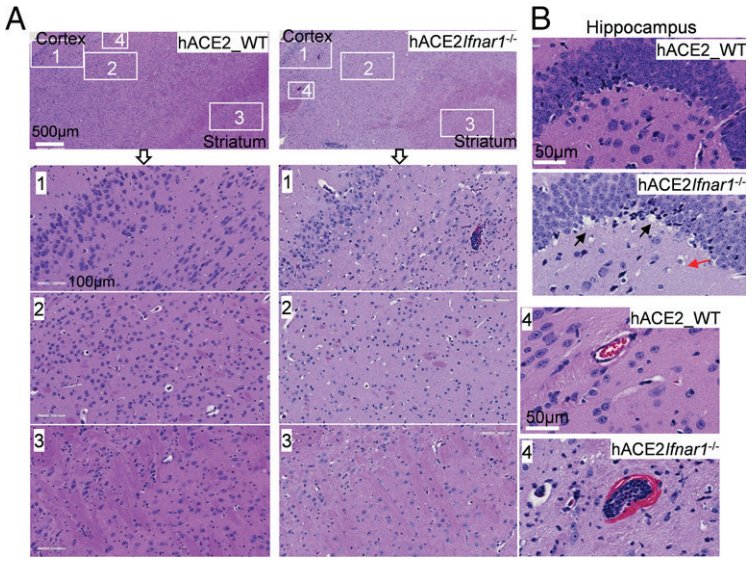

FIGURE 5. *Ifnar1* deficiency is associated with prominent pathological manifestations in the brain.

(**A** and **B**) Representative brain histopathology (H&E) of hACE2_WT (n = 4) and hACE2*Ifnar1*$^{-/-}$ mice (n = 7) at day 7 postinfection with 300 PFU/mouse of SARS-CoV-2 virus. Arrows indicate representative areas with multivacuolar structures (black) and neuropil vacuolation (red). Scale bars are indicated for each image.

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peripheral organs spleen and kidney. Although IFN-I signaling contributes to initial inhibition of viral replication in lung, it is not essential for viral control at the adaptive phase, as evidenced by 100-fold decreased viral burdens from day 4 to 7 after SARS-CoV-2 infection of hACE2*Ifnar1*$^{-/-}$ mice (Fig. 4). Thus, rather than a general defect in antiviral immunity at the initial infection site or systemically, the increased viral titers in the brains of hACE2*Ifnar1*$^{-/-}$ mice could reflect brain-specific viral invasion and replication in the absence of intact IFN-I signaling. In line with this, it has been shown that neuroinvasion by hepatotropic mouse hepatitis virus depends on the direct impairment of tight junctions, and IFN-β production by infected microvascular endothelial cells prevents transmission of blood-borne viruses to the brain (27).

In contrast, IFN-I has been shown to play an anti-inflammatory role by upregulating IL-10 and downregulating the IFN-γ response during influenza virus infection (16, 28). In the absence of IFN-I regulation, the increased inflammatory cytokine response could cause tissue damage and contribute to the disruption of the BBB, as known with other neurotropic viral and bacterial infections (29–31). Nonetheless, further studies are necessary to fully establish whether IFN-I signaling prevents SARS-CoV-2 neuroinvasion by restricting BBB permeability and/or inhibiting viral replication in the brain.

In conclusion, our results in this study indicate that IFN-I signaling is critical for preserving the integrity of CNS during SARS-CoV-2 infection. In agreement, it has been recently demonstrated that recessive deficiencies of IFN-I immunity underlie severe COVID-19 in unvaccinated children that are otherwise at lower risk for COVID-19 than unvaccinated adults (32). Thus, an improved understanding of mechanisms by which the immune system regulates protection against CNS infection will provide insights into the key virus–host interactions that decide acute and long-term sequelae of COVID-19.

DISCLOSURES

The authors have no financial conflicts of interest.

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