International Research Center for Infectious Diseases

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感染制御系・ウイルス学分野

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We focus on understanding how viruses are recognized by NLRP3 inflammasome and how the innate recognition receptor controls antigen-specific adaptive immune responses. We study immune responses to influenza viruses in the lung. Our recent focus also includes the study of how microbiota regulates adaptive immune responses to these pathogens. Our ultimate goal is to utilize the knowledge we gain through these areas of research in the rational design of effective vaccines for the prevention of infectious diseases.

1. TNF-α exacerbates SARS-CoV-2 infection by stimulating CXCL1 production from macrophages.

Kobayashi M, Kobayashi N, Deguchi K, Omori S, Nagai M, Fukui R, Song I, Fukuda S, Miyake K, and Ichinohe T.

Since most genetically modified mice are C57BL/6 background, a mouse-adapted SARS-CoV-2 that causes lethal infection in young C57BL/6 mice is useful for studying innate immune protection against SARS-CoV-2 infection. Here, we established two mouse-adapted SARS-CoV-2, ancestral and Delta variants, by serial passaging 80 times in C57BL/6 mice. Although young C57BL/6 mice were resistant to infection with the mouse-adapted ancestral SARS-CoV-2, the mouse-adapted SARS-CoV-2 Delta variant caused lethal infection in young C57BL/6 mice. In contrast, MyD88 and IFNAR1 KO mice exhibited resistance to lethal infection with the mouse-adapted SARS-CoV-2 Delta variant. Treatment with recombinant IFN-α/β at the time of infection protected mice from lethal infection with the mouse-adapted SARS-CoV-2 Delta variant, but intranasal administration of recombinant IFN-α/β at 2 days post infection exacerbated the disease severity following the mouse-adapted ancestral SARS-CoV-2 infection. Moreover, we showed that TNF-α amplified by type I IFN signals exacerbated the SARS-CoV-2 infection by stimulating CXCL1 production from macrophages and neutrophil recruitment into the lung tissue. Finally, we showed that intravenous administration to mice or hamsters with TNF protease inhibitor 2 alleviated the severity of SARS-CoV-2 and influenza virus infection. Our results uncover an unexpected mechanism by which type I interferon-mediated TNF-α signaling exacerbates the disease severity and will aid in the development of novel therapeutic strategies to treat respiratory virus infection and associated diseases such as influenza and COVID-19.

2. Prebiotic inulin ameliorates SARS-CoV-2 infection in hamsters by modulating the gut microbiome.

Song I, Yang J, Saito M, Hartanto T, Nakayama Y, Ichinohe T, Fukuda S.

Current treatment options for COVID-19 are limited, with many antivirals and immunomodulators restricted to the most severe cases and preventative care

limited to vaccination. As the SARS-CoV-2 virus and its increasing variants threaten to become a permanent fixture of our lives, this new reality necessitates the development of cost-effective and accessible treatment options for COVID-19. Studies have shown that there are correlations between the gut microbiome and severity of COVID-19, especially with regards to production of physiologically beneficial short-chain fatty acids (SCFAs) by gut microbes. In this study, we used a Syrian hamster model to study how dietary consumption of the prebiotic inulin affected morbidity and mortality resulting from SARS-CoV-2 infection. After two weeks of observation, we discovered that inulin supplementation attenuated morbid weight loss and increased survival rate in hamster subjects. An analysis of microbiome community structure showed significant alterations in 15 genera. Notably, there were also small increases in fecal DCA and a significant increase in serum DCA, perhaps highlighting a role for this secondary bile acid in conferring protection against SARS-CoV-2. In light of these results, inulin and other prebiotics are promising targets for future investigation as preventative treatment options for COVID-19.

Publications

Kobayashi M, Kobayashi N, Deguchi K, Omori S, Nagai M, Fukui R, Song I, Fukuda S, Miyake K, Ichinohe T. TNF-α exacerbates SARS-CoV-2 infection by stimulating CXCL1 production from macrophages. ***PLoS Pathog.*** 20(12):e1012776. 2024

Song I, Yang J, Saito M, Hartanto T, Nakayama Y, Ichinohe T, Fukuda S. Prebiotic inulin ameliorates SARS-CoV-2 infection in hamsters by modulating the gut microbiome. ***NPJ Sci Food.*** 8(1):18. 2024

Yang J, Song I, Saito M, Hartanto T, Ichinohe T, Fukuda S. Partially hydrolyzed guar gum attenuates symptoms and modulates the gut microbiota in a model of SARS-CoV-2 infection. ***Gut Microbiome (Camb)***. 6: e1. 2025

Kobayashi M, Kobayashi N, Deguchi K, Omori S, Ichinohe T. SARS-CoV-2 infection primes cross-protective respiratory IgA in a MyD88- and MAVS-dependent manner. ***NPJ Vaccines***. In press