

IMSUT Distinguished Professor Unit

Division of Virology

ウイルス感染部門

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Viruses can cause devastating diseases. The long-term goal of our research is to understand the molecular pathogenesis of viral diseases by using influenza virus, Ebola virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections as models. Interactions between viral and host gene products during viral replication determine the consequences of infection (i.e., the characteristics of disease manifestation, whether limited or widespread); hence, our research has centered on such interactions during these viral infections.

1. Neutrophil adhesion to vessel walls impairs pulmonary circulation in COVID-19 pathology.

Ueki H, Wang IH¹, Kiso M, Horie K^{2,3}, Iida S⁴, Mine S⁴, Ujie M, Hsu HW¹, Wu CH¹, Imai M, Suzuki T⁴, Kamitani W⁵, Kawakami E^{2,3,6}, Kawaoka Y.

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Microthrombus formation is associated with COVID-19 severity; however, the detailed mechanism remains unclear. In this study, we investigated mouse models with severe pneumonia caused by SARS-CoV-2 infection by using our in vivo two-photon imaging system. In the lungs of SARS-CoV-2-infected mice, increased expression of adhesion molecules in intravascular neutrophils prolonged adhesion time to the vessel wall, resulting in platelet aggregation and impaired lung perfusion. Re-analysis of scRNA-seq

data from peripheral blood mononuclear cells from COVID-19 cases revealed increased expression levels of *CD44* and *SELL* in neutrophils in severe COVID-19 cases compared to a healthy group, consistent with our observations in the mouse model. These findings suggest that pulmonary perfusion defects caused by neutrophil adhesion to pulmonary vessels contribute to COVID-19 severity.

2. SARS-CoV-2 virus lacking the envelope and membrane open-reading frames as a vaccine platform.

Kuroda M⁷, Halfmann PJ⁷, Uraki R, Yamayoshi S, Kim T⁷, Armbrust TA⁷, Spyra S⁷, Dahn R⁷, Babujee L⁷, Kawaoka Y. ⁷Influenza Research Institute, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI, 53711, USA.

To address the need for broadly protective SARS-CoV-2 vaccines, we developed an attenuated a SARS-CoV-2 vaccine virus that lacks the open reading frames of two viral structural proteins: the envelope (E) and membrane (M) proteins. This vaccine virus (Δ EM) replicates in a cell line stably expressing E and M but not in wild-type cells. Vaccination with Δ EM elicits a CD8 T-cell response against the viral spike and nucleocapsid proteins. Two vaccinations with

Δ EM provide better protection of the lower respiratory tissues than a single dose against the Delta and Omicron XBB variants in hamsters. Moreover, Δ EM is effective as a booster in hamsters previously vaccinated with an mRNA-based vaccine, providing higher levels of protection in both respiratory tissues compared to the mRNA vaccine booster. Collectively, our data demonstrate the feasibility of a SARS-CoV-2 Δ EM vaccine candidate virus as a vaccine platform.

3. Efficacy of baloxavir marboxil against bovine H5N1 virus in mice.

Kiso M, Uraki R, Yamayoshi S, Kawaoka Y

Since the first detection of highly pathogenic avian

influenza (HPAI) H5N1 (clade 2.3.4.4b) in U.S. dairy cattle in early 2024, the virus has spread rapidly, posing a major public health concern as the number of human cases continues to rise. Although human-to-human transmission has not been confirmed, experimental data suggest that the bovine H5N1 virus can transmit via respiratory droplets in ferrets, highlighting its pandemic potential. With no vaccines currently available, antiviral drugs remain the only treatment option. Here, we investigate the efficacy of the polymerase inhibitor baloxavir marboxil (BXM) against this virus in mice. We find that early treatment post-infection is effective, but delayed treatment significantly reduces BXM efficacy and increases the risk of BXM resistance, underscoring the importance of timely BXM administration for effective treatment.

Publications

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