PICREID Midterm Meeting
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Institut Pasteur, Paris, France

Evolution of SARS-CoV-2

Kei Sato, Ph.D.
Professor, Division of Systems Virology, Institute of Medical Science, The University of Tokyo, Japan.
Founder, The Genotype to Phenotype Japan (G2P-Japan) Consortium
KeiSato@g.ecc.u-tokyo.ac.jp

At the end of 2019, SARS-CoV-2, the causative agent of COVID-19, emerged in China. As of January 2023, SARS-CoV-2 is still ongoing pandemic: more than six hundred million cases of SARS-CoV-2 infection have been reported worldwide, with more than six million people dying of COVID-19. During the spreading worldwide, SARS-CoV-2 has been diversified, and these SARS-CoV-2 variants are considered to be the potential threats to the human society. To elucidate the virological characteristics of newly emerging SARS-CoV-2 variants in real-time, I have launched a consortium called "The Genotype to Phenotype Japan (G2P-Japan)" in January 2021. With the colleagues joining in G2P-Japan consortium, we have revealed the virological characteristics of SARS-CoV-2 variants such as Delta (Saito et al., Nature, 2022), Omicron BA.1 (Suzuki et al., Nature, 2022; Meng et al., Nature, 2022), BA.2 (Yamasoba et al., Cell, 2022), BA.5 (Kimura et al., Cell, 2022), BA.2.75 (Saito et al., Cell Host Microbe, 2022), BQ.1.1 (Ito et al., bioRxiv, 2022) and so on. In this talk, I will briefly introduce the scientific activity of G2P-Japan consortium and would like to discuss the possibility for international collaboration to combat the outbreaks and pandemic that will happen in the future.

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Emerging tick-borne bunyavirus infections

Keita Matsuno, DVM, Ph.D.
Associate professor, Division of Risk Analysis and Management, International Institute for Zoonosis Control, Hokkaido University.
The Genotype to Phenotype Japan (G2P-Japan) Consortium
matsuk@czc.hokudai.ac.jp

The order *Bunyavirales* is composed of a wide variety of tri-segmented negative-strand RNA viruses with over 400 species. Recent emergences of a series of tick-borne bunyavirus diseases raise attention to divergent bunyaviruses maintained in ticks. Severe fever with thrombocytopenia syndrome (SFTS) caused by SFTS virus grouped into the genus *Bandavirus*, family *Phenuiviridae*, is one of the emerging tick-borne bunyavirus diseases in Asian countries, including Japan since 2013. Interestingly, SFTS virus infection in felines causes a fatal disease similar to SFTS in humans; we found non-human lethal cases of SFTS virus infection in captive cheetahs naturally infected in a zoo. In 2019, we discovered a novel bunyavirus genetically classified into the genus *Orthonairovirus*, family *Nairoviridae*, tentatively designated as Yezo virus (YEZV) from a patient showing a febrile illness after a tick bite in Hokkaido, Japan. YEZV infection has been retrospectively confirmed in seven cases showing an acute febrile illness with leukocytopenia and thrombocytopenia after tick bite. YEZV is genetically closely related to orthonairoviruses causing human febrile illness in China. YEZV infection was also identified in ticks and wild animals in Hokkaido, suggesting endemic circulation. Our studies on emerging bunyavirus diseases will broaden the landscape of acute febrile illness with unknown causes.

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A zinc-finger-containing protein ZCCHC3 is a novel antiretroviral host factor

Akatsuki Saito, D.V.M., Ph.D.
Associate professor, Department of Veterinary Medicine, Faculty of Agriculture,
University of Miyazaki, Japan.
Member, The Genotype to Phenotype Japan (G2P-Japan) Consortium
sakatsuki@cc.miyazaki-u.ac.jp

Several anti-HIV-1 host factors have so far been identified, including APOBEC3s, and tetherin. Although these host factors show potent anti-HIV-1 activity, HIV-1 antagonizes these host factors by its accessory proteins. Identification and functional characterization of a novel anti-HIV-1 host factors can contribute to HIV-1 eradication.

Here we show that a zinc-finger-containing protein ZCCHC3 is a novel antiretroviral host factor. ZCCHC3 comprises of an N-terminal disordered region, middle folded domain, and characteristic C-terminal triple zinc-finger (ZFx3) motifs of CCHC type. Co-transfection of HEK293T cells with a ZCCHC3 expression vector and an HIV-1 molecular clone showed that ZCCHC3 inhibited production of progeny virions. Immunoblotting of viral particles demonstrated that ZCCHC3 was efficiently incorporated into viral particles mainly by interacting with Gag NC via its ZFx3 motifs. Finally, we investigated the antiretroviral spectrum of ZCCHC3 and showed that human ZCCHC3 blocked a wide range of lentiviruses including HIV-1, SIVmac, feline immunodeficiency virus, and equine infectious anemia virus. Also, ZCCHC3 molecules from other species showed similar antiviral activity. In conclusion, ZCCHC3 is a novel antiretroviral host factor which targets multiple steps of retroviral replication.