International Research Center for Infectious Diseases

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感染制御系

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Our special interest is focused upon searching for effective methods to protect or control viral infection by using accumulated knowledge based on molecular pathogenicity, and developing novel anti-viral drugs and attenuated strains for novel vaccines. The works have been conducted by close collaboration with Division of Molecular Virology, Department of Microbiology and Immunology.

1. Impact of the Interaction between Herpes Simplex Virus 1 ICP22 and FACT on Viral Gene Expression and Pathogenesis.

Shaocong Liu, Yuhei Maruzuru, Kosuke Takeshima, Naoto Koyanagi, Akihisa Kato, and Yasushi Kawaguchi

Facilitates chromatin transcription (FACT) interacts with nucleosomes to promote gene transcription by regulating the dissociation and reassembly of nucleosomes downstream and upstream of RNA polymerase II (Pol II). A previous study reported that herpes simplex virus 1 (HSV-1) regulatory protein ICP22 interacted with FACT and was required for its recruitment to the viral DNA genome in HSV-1 infected cells. However, the biological importance of interactions between ICP22 and FACT in relation to HSV-1 infection is unclear. Here, we mapped the minimal domain of ICP22 required for its efficient interaction with FACT to a cluster of five basic amino acids in ICP22. A recombinant virus harboring alanine substitutions in this identified cluster led to the decreased accumulation of viral mRNAs from UL54, UL38, and UL44 genes, reduced Pol II occupancy of these genes in MRC-5 cells, and impaired HSV-1 virulence in mice following ocular or intracranial infection. Furthermore, the treatment of mice infected with wild-type HSV-1 with CBL0137, a FACT inhibitor currently being investigated in clinical trials, significantly improved the survival rate of mice. These results suggested that the interaction between ICP22 and FACT was required for efficient HSV-1 gene expression and pathogenicity. Therefore, FACT might be a potential therapeutic target for HSV-1 infection.

2. Identification of a novel neurovirulence factor encoded by the cryptic orphan gene UL31.6 of herpes simplex virus 1

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Although the herpes simplex virus type 1 (HSV-1)

genome was thought to contain approximately 80 different protein coding sequences (CDSs), recent multi-omics analyses reported HSV-1 encodes more than 200 potential CDSs. However, few of the newly identified CDSs were confirmed to be expressed at the peptide or protein level in HSV-1-infected cells. Furthermore, the impact of the proteins they encode on HSV-1 infection is largely unknown. This study focused on a newly identified CDS, UL31.6. Re-analyzation of our previous chemical proteomics data verified that UL31.6 was expressed at the peptide level in HSV-1-infected cells. Antisera raised against a viral protein encoded by UL31.6 (pUL31.6) reacted with a protein with an approximate molecular mass of 37 kDa in lysates of Vero cells infected with each of three HSV-1 strains. pUL31.6 was efficiently dissociated from virions in high salt solution. A UL31.6-null mutation had a minimal effect on HSV-1 gene expression, replication, cell-to-cell spread, and morphogenesis in Vero cells; in contrast, it significantly reduced HSV-1 cell-to-cell spread in three neural cells but not in four non-neural cells including Vero cells. The UL31.6-null mutation also significantly reduced the mortality and viral replication in the brains of mice after intracranial infection, but had minimal effects on pathogenic manifestations in and around the eyes, and viral replication detected in the tear films of mice after ocular infection. These results indicated that pUL31.6 was a tegument protein and specifically acted as a neurovirulence factor by potentially promoting viral transmission between neuronal cells in the central nervous system.

3. MYBBP1A is required for efficient replication and gene expression of herpes simplex virus 1

Moeka Nobe, Yuhei Maruzuru, Kosuke Takeshima, Naoto Koyanagi, Akihisa Kato and Yasushi Kawaguchi

More than 100 different herpes simplex virus 1 (HSV-1) genes belong to three major classes, and their expression is coordinately regulated and sequentially ordered in a cascade. This complex HSV-1 gene expression is thought to be regulated by various viral and host cellular proteins. A host cellular protein, Myb-binding protein 1A (MYBBP1A), has been reported to be associated with HSV-1 viral genomes in conjunction with viral and cellular proteins critical for DNA replication, repair, and transcription within infected cells. However, the role(s) of MYBBP1A in HSV-1 infections remains unclear. In this study, we examined the effects of MYBBP1A depletion on HSV-1 infection and found that MYBBP1A depletion significantly reduced HSV-1 replication, as well as the accumulation of several viral proteins. These results suggest that MYBBP1A is an important host cellular factor that contributes to HSV-1 replication, plausibly by promoting viral gene expression.

Publications

Liu, S., Maruzuru, Y., Takeshima, K., Koyanagi, N., Kato, A., Kawaguchi, Y. Impact of the interaction between herpes simplex virus 1 ICP22 and FACT on viral gene expression and pathogenesis. J. Virol. 98: e00737-24, 2024.

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