News Release

Title: Genome-wide CRISPR screen for HSV-1 host factors reveals PAPSS1 contributes to heparan sulfate synthesis

Key Points

- Genome-wide CRISPR screen was performed for identifying host factors required for HSV-1 infection
- The host factors identified in this study included a series of genes involved in heparan sulfate biosynthesis
- Knockout of PAPSS1, one of our identified genes, reduced heparan sulfate (HepS) expression, consequently diminishing the binding of HSV-1 and several other HepS-dependent viruses (such as HSV-2, hepatitis B virus, and a human seasonal coronavirus).
- *PAPSS1* and its paralog *PAPSS2* functioned to be redundant during HepS biosynthesis

Summary

Drs. Yoshitaka Sato (Associate professor), Takeshi Suzuki (Pos-doc/Graduate student), and Hiroshi Kimura (Professor) at the Department of Virology, Nagoya University Graduate School of Medicine and collaborators performed a genome-wide CRISPR screen for HSV-1 host factors using near-haploid HAP1 cells. They demonstrated PAPSS1 as an essential factor for heparan sulfate biosynthesis and HSV-1 infection, and identified several other host factors also involved in both processes.

The report was published online in "*Communications Biology*", a journal in the Nature Publishing Group, on July 19, 2022.

Research Background

Herpes simplex virus type 1 (HSV-1) causes various diseases in humans, ranging from oral herpes and skin diseases to severe life-threatening encephalitis. HSV-1 is a "common/ubiquitous" virus. More than 70% of the world's population is infected with the herpes simplex viruses (including herpes simplex virus type 2). However, the relationship between this "common" virus and host factors is still poorly understood. Therefore, our research group attempted to identify host factors involved in herpes simplex virus type 1 infection by comprehensive single-gene knockout screening.

Research Results

In this study, the research group identified a series of genes involved in the biosynthesis of heparan sulfate and found that PAPSS1 (see Note #1) is a novel factor involved in HSV-1 infection. The knockout (KO) of *PAPSS1* was sufficient to abolish heparan sulfate

expression in HAP1 cells and consequently reduce the binding of various pathogenic viruses such as hepatitis B virus and human cold coronavirus.

Moreover, while the single KO of *PAPSS1* slightly affected HepS biosynthesis in some cell lines that expressed its paralog *PAPSS2*, the double KO of *PAPSS1* and *PAPSS2* resulted in reduced heparan sulfate expression and higher resistance against HSV-1 infections in human retinal pigment epithelial-1 cells, indicating a redundant role of *PAPSS1* and *PAPSS2* in HepS biosynthesis.

Research Summary and Future Perspective

Their findings confirmed the significance of heparan sulfate in HSV-1 infection and identified *PAPSS1* as the key factor for heparan sulfate biosynthesis. The genetic ablation of *PAPSS1* abolished the sulfated HepS expression on the cell surface in HAP1 cells. Furthermore, in some cells that express *PAPSS2*, *PAPSS2* compensated for *PAPSS1* in HepS biosynthesis. Therefore, this study provides new insights into host factors required for HSV-1 infection and HepS biosynthesis regulation.

Note #1: PAPSS1 (3'-Phosphoadenosine 5'-Phosphosulfate Synthase 1) is encoding the enzyme for synthesizing 3-prime-phosphoadenosine 5-prime-phosphosulfate (PAPS) which is the sulfate donor substrate for all sulfotransferase enzymes. In humans, PAPS is synthesized from ATP and inorganic sulfate by 2 isoforms, PAPSS1 and PAPSS2.

Funding information: This work was supported in part by grants from the Japan Society for the Promotion of Science (JSPS) KAKENHI (https://www.jsps.go.jp) (Grant Numbers JP16H06231 to Y.S., JP19H04829 to Y.S., JP21K15448 to Y.S., JP20K06551 to T.Mikami, JP20H03386 to H.Kitagawa; and JP20H03493 to H.Kimura); the JST (https://www.jst.go.jp) PRESTO (Grant Number JPMJPR19H5) to Y.S.; the Japan Agency for Medical Research and Development (AMED, https://www.amed.go.jp) (JP19jk0210023 to Y.S., JP21wm035042 to Y.S., JP19ck0106517 to Y.O., and JP20wm0325012 to T.Murata); the Takeda Science Foundation (https://www.takeda-sci.or.jp) to Y.S., Y.O., and T.Murata ; the Hori Sciences and Arts Foundation (https://www.hori-foundation.or.jp) to Y.S., T.Murata, and H.Kimura; the MSD Life Science Foundation (https://www.msd-life-science-foundation.or.jp) to Y.S.; the Aichi Health Promotion Foundation (https://ahpf.or.jp) to T.S.; and the Uehara Memorial Foundation (https://www.ueharazaidan.or.jp/) to H. Kimura; and the Chemo-Sero-Therapeutic Research Institute (https://www.kaketsuken.org) to H.Kimura. TS is supported by the Takeda Science Foundation scholarship.

Publication

Journal: Communications Biology
Title: Genome-wide CRISPR screen for HSV-1 host factors reveals PAPSS1 contributes to heparan sulfate synthesis

Authors: Takeshi Suzuki[1], Yoshitaka Sato[1,2,*], Yusuke Okuno[3], Fumi Goshima[1], Tadahisa Mikami[4], Miki Umeda[1], Takayuki Murata[1,5], Takahiro Watanabe[1], Koichi Watashi[6,7,8,9], Takaji Wakita[6], Hiroshi Kitagawa[4] and Hiroshi Kimura[1,*]

[1]Department of Virology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan
[2]PRESTO, Japan Science and Technology Agency (JST), Kawaguchi 332-0012, Japan
[3]Department of Virology, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601, Japan
[4]Laboratory of Biochemistry, Kobe Pharmaceutical University, Kobe 658-8558, Japan.
[5]Department of Virology and Parasitology, Fujita Health University School of Medicine, Toyoake 470-1192, Japan
[6]Department of Virology II, National Institute of Infectious Diseases, Tokyo 162-8640, Japan
[7]Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases, Tokyo 162-8640, Japan
[8]Department of Applied Biological Sciences, Tokyo University of Science, Noda 278-8510, Japan
[9]Institute for Frontier Life and Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
DOI: 10.1038/s42003-022-03581-9

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Com_220720.pdf