Genetic screening to fight the common childhood virus that causes hand, foot and mouth disease

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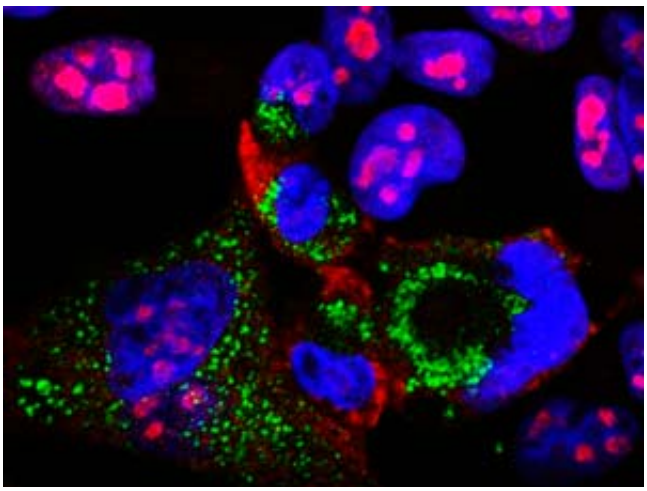

Enterovirus 71 infected cells: with the cell nuclei stained blue while the virus proteins are stained green. Credit: A*STAR Institute of Molecular and Cell Biology

The unavailability of antiviral medicines and vaccines has made outbreaks of hand, food and mouth disease (HFMD) caused by enterovirus 71 (EV71), a serious threat that affects millions worldwide. Now, an A*STAR comprehensive study has identified which human proteins in a cell are hijacked by EV71 and which try to resist its invasion. Clarifying these host-pathogen interactions could reveal new targets for antiviral therapeutics.

EV71 infections mainly affect children and can lead to aseptic meningitis, and long-term neurological complications, including polio-like paralysis. Since the EV71 genome encodes for just 11 proteins, it has cleverly evolved to exploit human cells to its advantage and guarantee its successful replication.

To check which human proteins facilitate or hinder EV71 replication, scientists at the A*STAR Institute of Molecular and Cell Biology have developed a gene 'atlas'. They screened 21,121 human genes, using a technique called small interfering RNA (siRNA). The team reported an extensive list of known and unknown classes of genes that play a role during EV71 infection.

Among the 256 so-called 'host factors' identified, several proteins help regulate the length of different stages of the cell cycle, like aurora kinase B (AURKB) and cyclin-dependent kinase 6 (CDK6). Interestingly, the virus seems to manipulate these proteins to favor its own replication. For example, by evicting CDK6 out of its workplace, the nucleus of the cell, EV71 could extend certain stages of the cell cycle to its own benefit.

Another sly mechanism used by this virus is to interfere with the cellular quality control process that discards abnormal or wrongly manufactured proteins. In this way, viral proteins can be produced inside the human cell, undisturbed.

The scientists focused on two host factors that were both shown to assist EV71 replication: N-glycanase 1 (NGLY1) and valosin-containing protein (VCP). Drugs that inhibit these two host factors also reduce the number of EV71-infected cells. VCP is probably held inside vesicular structures used by the virus to copy its genome, but it remains unknown how EV71 benefits from NGLY1.

"This is the first genome-wide siRNA screening for EV71-human

factors interaction and reveals the complex interplay between the virus and the proteins of a specific human cell line," points out Justin Jang Hann Chu, lead author of the study. "Some host factors we found are shared with picornaviruses and enteroviruses infections, while others are completely new and need to be further explored. This information opens a new chapter in the development of antiviral strategies for HFMD."

More information: Kan Xing Wu et al. Human genome-wide RNAi screen reveals host factors required for enterovirus 71 replication, *Nature Communications* (2016). DOI: 10.1038/ncomms13150

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