Haplotype Preference of Enterovirus 71 in Human Central Nerve System

Sheng-Wen Huang[1*], I-Hui Huang[2], Jen-Ren Wang[2]

[1.] Center of Infectious Disease and Signaling Reseach, National Cheng Kung University, [2.] Department of Medical Laboratory Science and Biotechnology, National Cheng Kung University

Background/Objective

Enterovirus 71 is a neurotropic RNA virus, which causes various clinical manifestations from mild symptoms such as hand-foot-and-mouth disease to severe neurological complications and death. In the transmission routes in human, enteroviruses infects hosts through oral-fecal route as primary infection sites and invades various tissues including central nerve system. RNA viral quasispecies, resulted from the rapid viral evolution with low fidelity of RNA polymerase in genome replication, contains diverse haplotypes which arises viral virulence depending on high genetic flexibility to easily adapt the environment selection pressure. To characterize the dynamic evolution genetic complexity, we here investigated the haplotypes of enterovirus 71 in various tissues from a fatal case.

Method

Amplified cDNA of enterovirus 71 strains isolated from various tissues were sequenced by next-generation sequencing. The identified mutation from sequencing results was examined its contribution to viral properties by using reverse genetics system.

Result

We found that viruses isolated from the tissues in the oral-fecal route contained more diverse haplotypes than other tissues. Dissecting the sequences of viral haplotypes displayed that high percentage of haplotypes had a non-synonymous substitution at VP1 protein in central nerve system tissues. This novel substitution obviously reduced thermal stability but increased RNA release efficiency and virus growth rate in human neuroblastoma and muscle rhabdomyosarcoma cells in vitro. Also, comparing haplotypes of the isolates from fatal and hand-foot-and mouth disease cases indicated that the isolates from fatal cases contained higher percentage of VP1 substitution.

Conclusion

Our results suggest that VP1 mutant haplotype increased in central nerve system because its survival advantage to infect human neuron cells. Analysis the viral haplotypes of clinical isolates might provide a potential predictor for the outcome of enterovirus 71-infected infants and children.