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Molecular mechanism of Japanese Encephalitis Virus entry into human neuronal cells

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Background & Aim: Japanese Encephalitis Virus (JEV) is a neurotropic virus, which causes Japanese Encephalitis (JE) in humans. The fatality rate of JE ranges from 20% to 30%, and 30% to 50% of survivors are left with severe neurological sequelae. The mechanism of JEV entry into neuronal cells to establish infection remains unclear. Previous studies once showed that JEV was endocytosed into neural stem cells by a clathrin-dependent pathway. But recent work indicated that JEV infects neuronal cells through a clathrin-independent endocytic pathway. The aim of the present study is to clarify host factor involved in JEV cell entry, and to reveal molecular mechanism of JEV entry into neuronal cells.

Materials & Methods: A targeted siRNA silencing screen using human endocytic/membrane trafficking library from Dharmacon was used to identify cellular factors involved in JEV entry. The siRNAs that inhibit JEV wild-type strain SA14 infection were identified in primary evaluation screening. Then, a pseudotype JEV (JEVpv) system was utilized to re-test those genes which are of inhibitory effect on JEV infection in the primary screening. Finally, specific inhibitors and dominant-negative mutants were used to examine their effect on endocytic pathways of JEV entry into neuronal cells.

Results: A total of 23 human genes with inhibitory effect on JEV infection were obtained in the primary screening. 15 out of the 23 host genes were identified as key molecules for JEV cell entry. Further studies showed that silencing 1 of the 15 genes, caveolin-1, resulted in a decrease in JEV viral entry. Silencing of dynamin-2 gene also exhibited an inhibitory effect on JEV entry. JEV entry was found to induce an increase in caveolin-1 phosphorylation. A large proportion of incoming JEV virions colocalized with caveolin-1 was observed in JEV-infected cells.

Conclusion: Caveolin-1 is a major defining marker of caveolae, and the crucial driver for caveolae formation. Dynamin-2 is a large GTPase which mediates the release of newly formed endocytic vesicles from the plasma membrane. Our data demonstrate that JEV takes advantage of caveolin-1 and dynamin-2 to establish its infection in neuronal cells. The findings might help better understand the JEV-host interaction, and provide with the possibility for design of novel anti-JEV agents.

Biography

Zhongtian Qi is a Professor of Microbiology in the Department of Microbiology at the Second Military Medical University in Shanghai, China. He has received his BS degree in Medicine from SMMU in 1977 and MS degree in Medical Microbiology in 1981 and a PhD degree in Clinical Immunology in 1993 from the same university. His research interests focus on pathogenesis and immunity of medically important viruses, especially on hepatitis virus, Japanese Encephalitis Virus and dengue virus.

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