エンテロウイルス68型の疫学,抗原性および受容体結合性に関する解析

（書式１８）課程博士

学　位　論　文　要　約

博士論文題目　エンテロウイルス 68 型の疫学,抗原性および受容体結合性に関する解析

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Increased detection of Enterovirus 68 (EV68) among patients with acute respiratory infections was reported from different parts of the world in the late 2000s since its first detection from pediatric patients with lower respiratory infections in 1962. However, the underlying mechanisms for such increasing trend are still unknown.
Therefore, in the study, I first aimed at studying the etiological significance and the molecular evolution of circulating EV68 strains in the Philippines.
Nasopharyngeal swabs were collected from 5,240 patients with acute respiratory infections in the Philippines from June 2009 to December 2011. EV68 was detected by polymerase chain reaction (PCR) targeting for 5' untranslated region (5'UTR), viral protein 1 (VP1), and VP4/VP2. Phylogenetic trees were generated using the obtained sequences.
Of the 5,240 tested samples, 12 EV68 positive cases were detected between August and December in 2011 (detection rate, 0.23%). The detection rate was higher among inpatients than outpatients (p<0.0001). Among VP1 sequences detected from 7 patients in 2011, 5 in lineage 2 were diverged from those detected in the Philippines in 2008, however, 2 in lineage 3 were not diverged from strains detected in the Philippines in 2008 but closely associated with strains detected in the United States. Combined with my previous report, EV68 occurrences were observed twice in the Philippines within the last four years. EV68 detections might be occurring in cyclic patterns, and viruses might have been maintained in the community while some strains might have been newly introduced.
In the study, I also tested serum samples collected from pneumonia patients whose nasopharyngeal specimens were positive for EV68. Out of total 28 nasopharyngeal sample positive pediatric patients, EV68 were detected in serum samples among 12 (43%) patients aged between 1 and 4 years. My results suggest that EV68 can cause viremia by which the virus may exhibit systemic manifestations.

Additionally, I studied the antigenicity and receptor binding properties of EV68 detected in recent years in comparison to the prototype strain of EV68: Fermon strain. I first performed neutralization (NT) and hemagglutination inhibition (HI) tests using antisera generated for EV68 strains detected in recent years. I found that Fermon strain had lower HI and NT

titers than EV68 strains detected in recent years. The HI and NT titers were also significantly different between strains of different genetic lineages among EV68 strains detected in recent years. I further studied receptor binding specificities of EV68 strains for sialyloligosaccharides using glycan array. In glycan array analysis, all tested EV68 strains showed affinity to α2-6 linked sialic acids (SAs) compared to α2-3 SAs. My study demonstrated that emergence of strains with different antigenicity is the possible mechanisms for the increased detections of EV68 in recent years. Additionally, I revealed that EV68 preferably binds to α2-6 SAs which suggested that EV68 might have affinity to upper respiratory tract.