

経鼻インフルエンザワクチン接種者由来広域中和抗体のエスケープ変異体ウイルスの解析

Analysis of escape mutant viruses of an intranasal influenza vaccine-derived broadly neutralizing antibody clone

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【Background】

Intranasal inactivated influenza vaccine (IIV) could induce secretory IgA antibodies in the mucosal surface of the upper respiratory tract and protect host from virus infection. Due to the occasional antigenic mismatches between circulating virus and vaccine virus, whether vaccine strategies could induce influenza virus broadly neutralizing antibodies (bnAbs) is an important issue. In this study, an influenza bnAb was obtained from an IIV recipient and its epitope was identified by analysis of escape mutant viruses.

【Materials and Methods】

An influenza bnAb clone, F11 was selected by ELISA and virus neutralization

assay. Two escape mutants (mutant C1 and G6) were generated by serial passages in the presence of F11. Binding activity of F11 to mutant HAs were measured by ELISA and surface plasmon resonance (SPR) analysis. Molecular models of HA trimers were constructed by homology modeling. Molecular dynamics simulation (MDS) was performed with the AMBER program package using TSUBAME 3.0 supercomputer.

【Results】

Escape mutants, C1 and G6, acquired single amino acid substitutions in the HA stalk (T333K and G480D, respectively). The mutations induced marked reduction in binding affinity of HA trimers to F11 in parallel with major structural changes in the hydrophobic groove in the HA stalk. The structural changes included destruction of hydrophobic groove (T333K) and alterations in fluctuation profiles around the hydrophobic groove (T333K and G480D). Interestingly, G480D was located outside the hydrophobic groove.

【Discussion】

These results suggest that the epitope of F11 is located around the hydrophobic groove of the HA stalk and that an amino acid substitution apart from antibody epitope can remotely control antibody binding.

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