

Poster presentation

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P09-16. A primary R5 isolate undergoes different escape pathway during *in vitro* selection with low or high concentration of an anti-V3 monoclonal antibody

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Background

The mechanisms of immune escape from neutralizing antibody are not fully understood for primary HIV-1 isolates with R5 phenotype. Using two different conditions of the anti-V3 humanized monoclonal antibody (Mab) KD-247 for selecting escape mutants we analyzed the mechanism of escape pathway of a primary R5 virus.

Methods

We induced escape variants by exposing a neutralization-sensitive primary R5 isolate, HIV-1_{MTA} to increasing concentrations of KD-247 in PM1/CCR5 cells. The virus was initially exposed 1 or 0.05 µg/ml of KD-247 and was serially passaged up to 1000 µg/ml. We determined the changes in the amino acid (aa) sequences of gp120-encoding region at each passage and monitored neutralization sensitivity of the passaged virus by WST-8 assay. To compare replication fitness of the escape mutants a competition assay was performed in the presence or absence of KD-247.

Results

Under high KD-247 pressure (1 µg/ml), a substitution of aa in V3 tip (GPGR→GQGR, MTA_{P313Q}) was observed at passage 2 (p2) and was subsequently detected in virtually all the clones examined at p5 (20 µg/ml). On the other hand, under relatively low KD-247 pressure (0.05 µg/ml), another substitution in V3 tip (GPGR→GPGK, MTA_{R315K}) was emerged at p5 (0.4 µg/ml) and was dominated in virtually all subsequent clones at p14 (10 µg/ml). These

escape mutants were found to have highly resistant phenotype to KD-247. A series of competition assay of the mutants revealed that MTA_{R315K} replicates better than MTA_{P313Q} in the absence of KD-247. On the other hand, MTA_{P313Q} dominated over MTA_{R315K} in the presence of KD-247.

Conclusion

The viral fitness to the cell and the resistance to the specific antibodies are major factors contributing the virus escape from neutralizing antibodies. Our results demonstrated the primary R5 isolate HIV-1_{MTA} underwent different escape pathway dependent on the concentration of the antibody.