Nuclear Exportation in Avian Influenza Virus Adaptation to Human Cells

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Background/Objective
To define genetic determinant that responsible for nuclear export phenotype during interspecies transmission of avian influenza viruses to human cells

Method
15 subtypes of avian influenza A viruses were infected in human lung and chicken cell lines. The virus that showed high HA titer in chicken cells but low titer in human lung cells, H7N1, was selected for the determination of nuclear exportation efficiency in several cell lines from different origin by immunofluorescence assay. H7N1 was serially passages in human lung cells until it can infect the cells and export viral protein efficiently. After that, reverse genetic virus was generated in order to identify genetic determinant that responsible for nuclear exportation phenotype of the virus.

Result
The H7N1 virus showed nuclear export defect phenotype in several human cell lines but not in chicken or mammalian cells indicates the role of nuclear exportation during viral adaptation to human host. After 10 passages in human lung cells, the adapted H7N1 (H7N1:P10) can export viral nucleoprotein efficiently. Reverse genetic virus indicated that viral matrix protein M1 responsible for nuclear export defect phenotype of the parental H7N1, while a single mutation alanine to serine at position 227 of H7N1:P10 can reconstitute the nuclear export efficiency of the virus.

Conclusion
Amino acid position 227 of M1 locates at C-terminal domain that binds to viral ribonucleoprotein (vRNP) complex of the virus during nuclear exportation. Alanine at this position might affect the vRNP binding of M1 leading to unsuitable nuclear export complex formation. In addition, M1 is subjected to interact with cellular histones during nuclear exportation in order to allow access to a Crm1-dependent nuclear export partway. Therefore, it was hypothesized that alanine at position 227 may interfere the interaction between viral M1 and cellular histone during nuclear exportation in human cells