論文の内容の要旨

論文題目　Genetic compatibility between the pandemic (H1N1) 2009 and contemporary influenza viruses: implications for the generation of the next pandemic.

（パンデミック（H1N1）2009 ウイルスと季節性及び高病原性鳥インフルエンザウイルスの遺伝子適合性の解析－新たなパンデミック発生におけるその意義）

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Influenza is a major public health concern, causing annual epidemics with considerable morbidity and mortality worldwide, and sporadic pandemics. The influenza A virus genome comprises eight single-stranded RNA segments. This feature allows genetic reassortment, which is important for influenza virus evolution, contributing to the genesis of pandemic influenza viruses via antigenic shift. A thorough understanding of the factors that govern reassortment is, therefore, essential to our ability to predict and respond to future influenza pandemics.

Since 1997, highly pathogenic avian H5N1 influenza viruses have consistently crossed the species barrier and infected humans with a high lethality rate, and it is feared that they could acquire the ability to transmit efficiently among humans, possibly through reassortment, thus acquiring pandemic potential. The emergence of the pandemic (H1N1) 2009 influenza A virus (pdm2009) may represent a

new opportunity for such reassortment. Moreover, the possibility of enhanced virus growth of pdm2009 through reassortment with contemporary seasonal viruses cannot be overlooked.

With the ultimate goal of shedding light on the factors that may shape the emergence of the next pandemic virus, I have studied different aspects of reassortment in influenza viruses, with an emphasis on the genetic compatibility between pdm2009 virus and contemporary seasonal viruses and highly pathogenic avian H5N1 influenza viruses. By co-infecting cells with pdm2009 and a contemporary human H5N1 virus isolate I found that these two viruses had a high level of genetic compatibility, since about 85% of the resulting progeny virions were reassortants. A replicon assay showed that all possible combinations of the ribonucleoprotein complex components between the two viruses had substantial activity, and studies in human airway epithelium cell lines revealed that reassortants between pdm2009 and H5N1 viruses had high growth capability, with some reassortants showing enhanced growth kinetics in human lung cell lines relative to the wild-type parental viruses. These findings suggest that upon co-infection of a susceptible host with pdm2009 and H5N1 viruses, reassortment is likely to occur, with the possible generation of pandemic H5N1 viruses. Moreover, reassortant viruses produced by using reverse genetics that contained the HA of a seasonal H1N1 virus and the NA and M genes of pdm2009 virus showed enhanced growth capability over their wild-type parental viruses, suggesting that the emergence of such viruses could also represent a threat. However, a factor that restricted influenza virus genetic reassortment was also identified, because a polymerase complex containing a pdm2009 PB2 on a seasonal H1N1 virus background showed restricted polymerase activity that led to impaired virus viability. The results of adaptation experiments and a replicon assay pointed to the cooperation between PB2 and PB1 as a restricting factor for reassortment of influenza viruses.

The research I present here contributes to our understanding of the factors that govern reassortment in influenza viruses. This knowledge may provide insights into the future of pandemic influenza, thereby allowing more effective surveillance, preparedness, prevention, and control measures.