Internal genes of a highly pathogenic H5N1 influenza virus determine high viral replication in myeloid cells and severe outcome of infection in mice

Collaborating with Prof. Wendy Barclay from the Section of Virology, Department of Medicine, Imperial College London, the research team directed by Prof. Cao Bin (曹彬) from the Department of Respiratory Medicine, Capital Medical University; Center for Respiratory Diseases, Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China, recently reported that human and avian influenza viruses are differently controlled by host factors in alternative cell types; internal gene segments of avian H5N1 virus uniquely drove high viral replication in myeloid cells, which triggered an excessive cytokine production, resulting in severe immunopathology. The work was supported by the National Natural Science Foundation of China and published in *PLoS Pathog* (2018, 14(1): e1006821).

The severity of the next influenza virus pandemic will be determined by the nature of the virus that emerges from an animal source and acquires an airborne transmissible phenotype. The highly pathogenic avian influenza (HPAI) H5N1 influenza virus has been a public health concern for more than a decade because of its frequent zoonoses and the high case fatality rate associated with human infections. Severe disease following H5N1 influenza infection is often associated with dysregulated host innate immune response also known as cytokine storm, but the virological and cellular basis of these responses has not been clearly described. In this research, we aimed to understand the virological mechanism behind the cytokine storm, and particularly the contribution of internal gene segments that encode the viral polymerase and the non-structural proteins, since these might be retained in a pandemic virus.

To avoid the complication that different viral surface proteins, HA and NA, might affect cell tropism and immune responses *in vitro* and *in vivo*, they rescued a series of 6 ∶ 2 reassortant viruses that combined a a A/Puerto Rico/8/34 (PR8) HA/NA pairing with the internal gene segments from human adapted H1N1, H3N2, or avian H5N1 viruses. They found that mice infected with the virus with H5N1 internal genes suffered severe weight loss associated with increased lung cytokines but not high viral load. This phenotype did not map to the NS gene segment. Instead they discovered that the internal genes of H5N1 virus supported a much higher level of replication of viral RNAs in myeloid cells *in vitro*, but not in epithelial cells and that this was associated with high induction of type I IFN in myeloid cells. They also found that *in vivo* during H5N1 recombinant virus infection cells of haematopoetic origin were infected and produced type I IFN and proinflammatory cytokines.

Taken together their data infer that human and avian influenza viruses are differently controlled by host factors in alternative cell types; internal gene segments of avian H5N1 virus uniquely drove high viral replication in myeloid cells, which triggered an excessive cytokine production, resulting in severe immunopathology. This finding may guide future therapeutic options for viruses that have recently crossed into humans from birds.

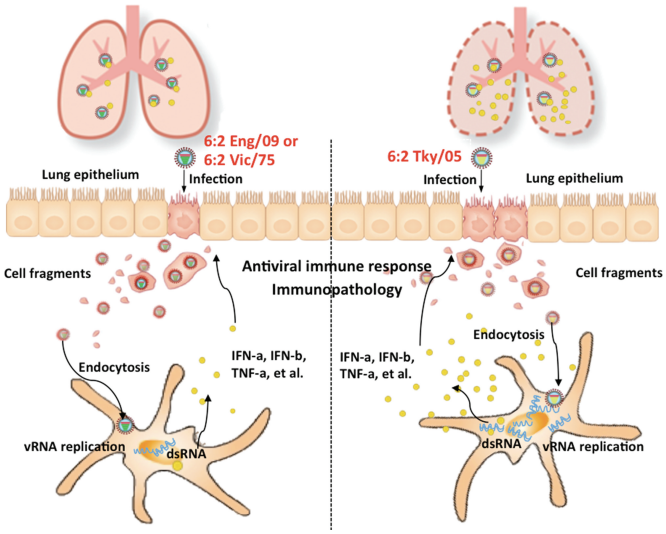

Figure Shematic of the features in the lung of mice after infection with 6 ∶ 2 Eng/09 or 6 ∶ 2 Vic/75, 6 ∶ 2 Tky/05, respectively.