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Tropism of H7N9 influenza viruses in the human respiratory tract

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The first reports of human infection with avian influenza A H7N9 appeared 3 months ago, and since then there have been more than 130 confirmed cases with 43 fatalities.[1] Until this outbreak, H7 subtype influenza virus infection in human beings was typically associated with mild respiratory illness or conjunctivitis. The atypical association of H7N9 virus infection with severe human respiratory illness and death clearly represents a new and pressing public health threat. The high incidence of pneumonia and acute respiratory distress syndrome among severe and fatal cases[2] is similar to H5N1 virus infection and necessitates a greater understanding of the ability of this virus subtype to target the human respiratory tract.

In *The Lancet Respiratory Medicine*, Michael C W Chan and colleagues[3] report the cell tropism and induction of innate host responses of two H7N9 viruses in several in-vitro and ex-vivo cultures, representative of, or derived from, the upper and lower human respiratory tract. Compared with other avian influenza viruses, Chan and colleagues find a heightened ability for the H7N9 viruses to replicate in human bronchus and lung, with induction of proinflammatory cytokines and chemokines in respiratory cells playing a lesser part in the overall pathogenesis of this virus subtype. These analyses support several initial clinical and epidemiological findings[2] and provide greater insight into the remarkable ability of this low pathogenic avian influenza virus to cause severe human disease.

The findings of Chan and colleagues contribute to several areas of ongoing investigation. The two phylogenetically distinct H7N9 viruses examined, which differ in key aminoacids in the virus haemagglutinin known to modulate receptor binding,[4] displayed comparable infectivity and tropism in this study, suggesting that these residues do not dramatically alter the pathogenicity of H7N9 disease; in-vivo studies in the ferret model corroborate this finding.[5] While pneumonia and acute respiratory distress syndrome have been associated with severe human disease after both H5N1 and H7N9 virus infection, the observation that H7N9 viruses exhibit an enhanced ability to infect the bronchus and lung compared with H5N1 viruses offers an avenue for further investigation and potential therapeutic application against this virus subtype. Examination of the relative ability of H5N1 and H7N9 viruses to dysregulate host innate immune responses in human tissues, revealing that H7N9 viruses

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elicit a greater induction of proinflammatory cytokines and chemokines compared with 2009 pandemic H1N1 but not H5N1 virus, similarly provides guidance for treatment and control.

Still, the study by Chan and colleagues raises as many questions regarding the pathogenicity of H7N9 viruses as it addresses. The unusual age distribution among H7N9 human cases remains unanswered; expansion of tropism and infectivity studies to include tissues collected from case patients representing a greater distribution of age and health statuses might shed light on this characteristic. Second, this study adds to growing evidence that Eurasian-lineage H7 influenza viruses, H7N9 viruses among them, are poor inducers of innate immune responses in human respiratory tissues.[6] Understanding the ability of H7 viruses to evade host responses has implications for both the pathogenesis of human disease and the poor immunogenicity observed in clinical trials of H7 vaccine candidates.[7] Third, the absence of conjunctivitis among human cases of H7N9 infection is in stark contrast with the previous association of this virus subtype with ocular disease. Extension of the tropism and host response studies conducted by Chan and colleagues to human conjunctival ex-vivo cultures, which have been shown by the investigators to support replication of many human and avian influenza viruses,[8] could further our understanding of this virus property.

The efficiency of H7N9 viruses to replicate in lower respiratory tract ex-vivo cultures reported by Chan and colleagues is in agreement with recent in-vivo studies that show high viral titres in the lungs of H7N9 virus-infected ferrets.[5,9] These ferret studies also revealed efficient transmission of H7N9 virus to naive animals in the presence of direct contact, with reduced transmission detected by the airborne route. Interestingly, H5N1 viruses replicate to comparably high titres throughout the ferret respiratory tract and cause severe respiratory disease in human beings, but unlike H7N9 viruses, do not transmit efficiently to naive ferrets. This finding could be due, in part, to the lack of binding to α-2,6-linked sialic acid analogues among H5N1 viruses and diminished production of inflammatory mediators in the ferret nasal passages associated with sneezing and rhinorrhoea after infection with H5N1 viruses.[10] Notably, H7N9 viruses isolated from human beings possess a greater affinity for α-2,6-linked sialic acid analogues compared with avian H7 and H5 subtype viruses, while maintaining robust binding to α-2,3-linked sialic acid analogues.[4,11] The findings of Chan and colleagues support the need for future studies investigating the interplay between H7N9 virus tropism, receptor binding specificity, the magnitude of local innate immune responses, and transmissibility.

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