BRIEF COMMUNICATIONS

Influenza virus receptors in the human airway

Avian and human flu viruses seem to target different regions of a patient's respiratory tract.

Although more than 100 people have been infected by H5N1 influenza A viruses, human-to-human transmission is rare[1]. What are the molecular barriers limiting human-to-human transmission? Here we demonstrate an anatomical difference in the distribution in the human airway of the different binding molecules preferred by the avian and human influenza viruses. The respective molecules are sialic acid linked to galactose by an α-2,3 linkage (SAα2,3Gal) and by an α-2,6 linkage (SAα2,6Gal)[2]. Our findings may provide a rational explanation for why H5N1 viruses at present rarely infect and spread between humans although they can replicate efficiently in the lungs.

SAα2,3Gal molecules have been found on cells artificially differentiated from isolated human tracheal and bronchial cells *in vitro*[3]. But the anatomical distribution and prevalence of SAα2,3Gal and SAα2,6Gal in the human airway was unknown. Using lectins specific for SAα2,3Gal and SAα2,6Gal, we found that SAα2,6Gal is dominant on epithelial cells in nasal mucosa, with SAα2,3Gal being occasionally detected (for details and methods, see supplementary information). Epithelial cells in the paranasal sinuses, the pharynx, the trachea[4] and the bronchi mainly express SAα2,6Gal (Fig. 1, and see supplementary information). In the terminal and respiratory bronchioles, epithelial cells also express SAα2,6Gal sialyloligosaccharides.

SAα2,3Gal was found on non-ciliated cuboidal bronchiolar cells at the junction between the respiratory bronchiole and alveolus, however, and a substantial number of cells lining the alveolar wall also expressed this molecule. The SAα2,3Gal-positive alveolar cells also reacted to an antibody against surfactant protein A; this suggests that they were alveolar type-II cells (which express surfactant protein A). Alveolar type-II cells have been shown to be infected with H5N1 virus in a patient[5].

Human-derived viruses that preferentially recognize SAα2,6Gal bound extensively to epithelial cells in the bronchi and, to a lesser degree, to alveolar cells; by contrast, avian viruses that preferentially recognize SAα2,3Gal bound extensively to alveolar cells but less widely to bronchial epithelial cells (see supplementary information). It is interesting that the A/Hong Kong/213/03 (H5N1) virus, which was isolated from a human and recognizes both SAα2,3Gal and SAα2,6Gal (ref. 6), bound

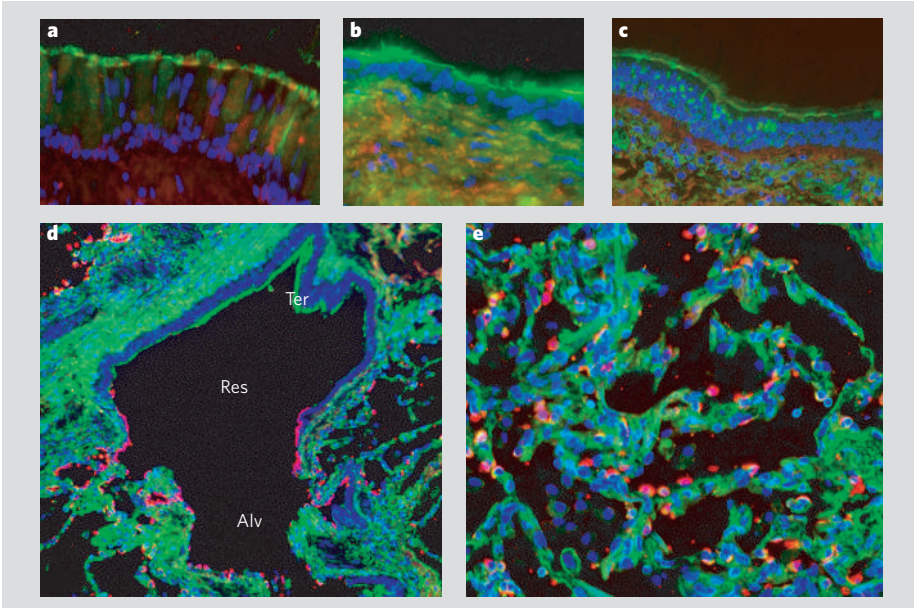

Figure 1 | Reactivity of human respiratory tissues with lectins specific for different sialic acid linkages. **a,** Nasal mucosa; **b,** paranasal sinuses; **c,** bronchus; **d,** bronchiole; **e,** alveolus. Res, respiratory bronchiole (adjacent to alveoli); Ter, terminal bronchiole (distal to alveoli); Alv, alveolus. Green, reaction with *Sambucus nigra* lectin, indicating the presence of sialic acid linked to galactose by an α2,6-linkage (SAα2,6Gal). Red, reaction with *Maackia amurensis* lectin, indicating the presence of SAα2,3Gal. Cells were counterstained with DAPI (4,6-diamidino-2-phenylindole).

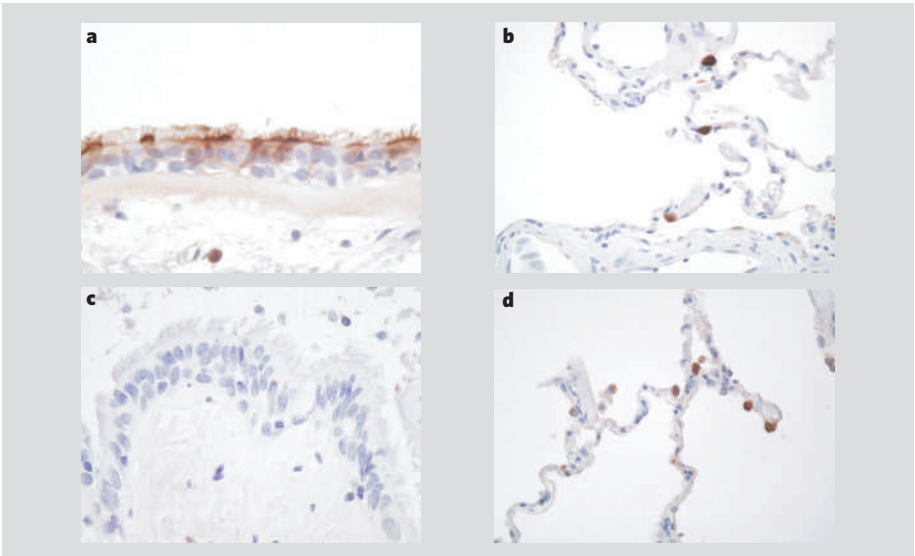

Figure 2 | Infection of human respiratory tissue by influenza A viruses. **a,** Extensive infection of bronchial epithelial cells by human A/Kawasaki/173/01 (H1N1) virus. **b,** Infection of alveolar cells by the human virus. **c,** Bronchial epithelial cells are not infected by A/duck/Mongolia/301/01 (H3N2) virus. **d,** Infection of alveolar cells by the avian virus. The results obtained with other human viruses, A/Yokohama/2057/03 (H3N2) and A/Kawasaki/176/02 (H1N1), were similar to those obtained with A/Kawasaki/173/01, and those obtained with the avian viruses A/duck/Czechoslovakia/56 (H4N6) and A/duck/Vietnam/5001/05 (H5N1) were similar to those obtained with A/duck/Mongolia/301/01. Infected cells are stained brown.

extensively to both bronchial and alveolar cells.

Human-derived viruses preferentially recognizing SAα2,6Gal efficiently infected epithelial cells lining the bronchi and alveolar cells (Fig. 2a, b), whereas avian viruses preferentially recognizing SAα2,3Gal infected alveolar cells but not bronchial epithelial cells (Fig. 2c, d, and see supplementary information). As shown in a virus-binding assay, A/Hong Kong/213/03 infected both alveolar cells and epithelial cells in bronchi (see supplementary information). Although not quantitative, these results indicate that there could be functional significance in the preferential expression of SAα2,3Gal and SAα2,6Gal molecules on human airway cells.

Our findings indicate that although H5N1 viruses preferentially recognizing SAα2,3Gal can be transmitted from birds to humans, they can replicate efficiently only in cells in the lower region of the respiratory tract, where the avian-virus receptor is prevalent. This restriction may contribute to the inefficient human-to-human transmission of H5N1 viruses seen so far, and indicates that unimpeded transmission of the virus might require acquisition of the ability to recognize SAα2,6Gal. This change would enable the virus to replicate in the upper region of the respiratory tract, where it could be readily spread by sneezing and coughing. Mutations in the viral haemagglutinin molecule would be necessary to confer SAα2,6Gal-binding ability on H5N1 avian viruses, although amino-acid substitutions in other viral proteins, including PB2 (refs 7, 8), may be required to confer pandemic potential on avian viruses that can efficiently replicate in humans.

Kyoko Shinya*†‡§, Masahito Ebina||, Shinya Yamada†, Masao Ono¶, Noriyuki Kasai‡, Yoshihiro Kawaoka*†#☆

*Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, Wisconsin 53706, USA
e-mail: kawaokay@svm.vetmed.wisc.edu
†Division of Virology, Department of Microbiology and Immunology, #International Research Center for Infectious Diseases, Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan
‡Institute for Animal Experimentation, ||Respiratory Oncology and Molecular Medicine, Institute of Development, Aging, and Cancer, ¶Department of Pathology, Graduate School of Medicine, Tohoku University, Sendai, Miyagi 980-8575, Japan
☆Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan
§Present address: The Avian Zoonosis Research Centre, Tottori University, Tottori 680-8550, Japan

1. Beigel, J. H. *et al. N. Engl. J Med.* **353,** 1374–1385 (2005).
2. Rogers, G. N. & Paulson, J. C. *Virology* **127,** 361–373 (1983).
3. Matrosovich, M. N., Matrosovich, T. Y., Gray, T., Roberts, N. A. & Klenk, H. D. *Proc. Natl Acad. Sci. USA* **101,** 4620–4624 (2004).
4. Baum, L. G. & Paulson, J. C. *Acta Histochem.* **40** (suppl.), 35–38 (1990).
5. Uiprasertkul, M. *et al. Emerg. Infect. Dis.* **11,** 1036–1041 (2005).
6. Shinya, K. *et al. J. Virol.* **79,** 9926–9932 (2005).
7. Naffakh, N., Massin, P., Escriou, N., Crescenzo-Chaigne, B. & van der Werf, S. *J. Gen. Virol.* **81,** 1283–1291 (2000).
8. Hatta, M., Gao, G., Halfmann, P. & Kawaoka Y. *Science* **293,** 1840–1842 (2001).

Supplementary information accompanies this communication on *Nature*'s website.
Received 12 Feb 2006; accepted 9 March 2006.
Competing financial interests: declared none.
doi:10.1038/440435a

ECOLOGY

Human role in Russian wild fires

Anomalies in temperature and precipitation in northern Russia over the past few years have been viewed as manifestations of anthropogenic climate change[1], prompting suggestions that this may also account for exceptional forest fires in the region[2,3]. Here we examine the number of forest-fire events across the boreal Russian Federation for the period 2002 to 2005 in 'intact' forests, where human influence is limited, and in 'non-intact' forests, which have been shaped by human activity[4]. Our results show that there were more fires in years during which the weather was anomalous, but that more than 87% of fires in boreal Russia were started by people.

Since the last Ice Age, fire has been the main process that has disturbed the physical features of the boreal biome. Three major fire seasons have occurred recently in Russia: a total of 6.9, 7.5 and 14.5 million hectares (ha) were burned in 1998 (ref. 5), in 2002 (ref. 5) and in 2003 (ref. 6), respectively. Large climate anomalies occurred during this period[7] that increased the likelihood of fire ignition and propagation. In combination, this evidence points to a serious impact of climate change on Russian forests[2,3], although fires are considered to be caused predominantly by humans in 'normal' years[4,8].

Large areas of intact forest still exist in Russia; it can be assumed that human influence on these areas is limited. Using satellite data to locate fires, we estimated the number of fire events in these intact forests and in forests more affected by humans in order to assess the specific impact of climate anomalies

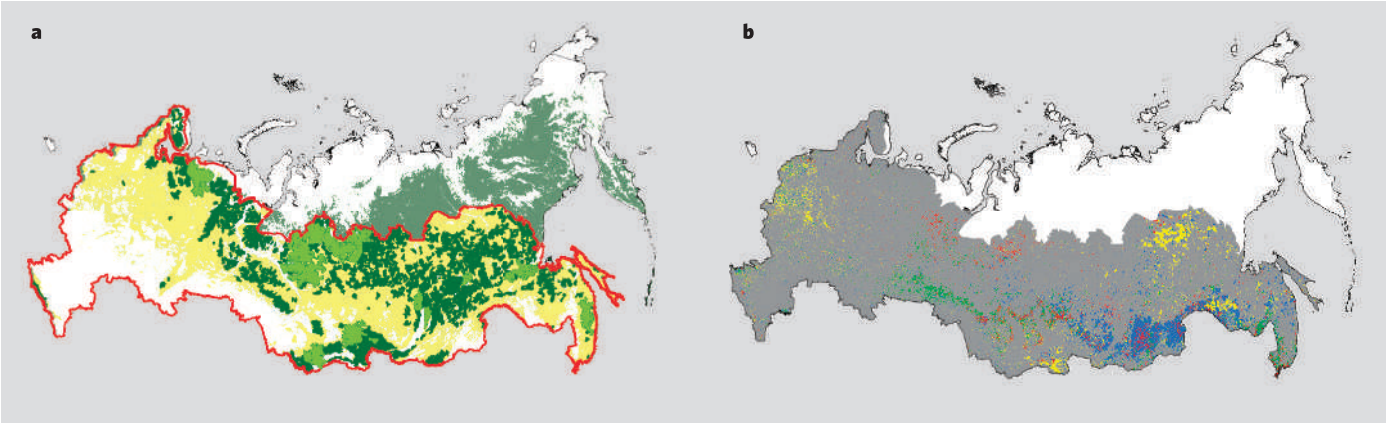

Figure 1 | Maps of the Russian Federation showing areas of intact forest and the locations of forest fires over 2002–2005. a, The 'intact' forest areas (dark green) of the region are defined[4] as being situated within the forest zone, having a size exceeding 50,000 ha and a width of 10 km at the narrowest point. They contain a contiguous mosaic of natural ecosystems, are not fragmented by infrastructure, show no signs of significant transformation by humans, and have a natural fire regime. Light green areas, 'most-intact' forest (a subset of intact forest; see text); yellow; non-intact forest; grey-green, forest outside the study area. The study area is outlined in red. The northern limit for the region covered by the atlas[4] excludes all tundra ecosystems; the Kamchatka region was excluded from our study zone. **b,** Locations of active fires in 2002 (yellow), 2003 (blue), 2004 (green) and 2005 (red); 2002 and 2003 were severe years. Fire dots are overlaid for years from 2002 to 2005, so fires from earlier years may be obscured by later years (dot size is exaggerated for display purposes). The study area is shaded in grey.