little or no preexisting immunity is a fundamental property of pandemic strains (*6*, *7*). Most threatening is the possibility of another pandemic, similar to that experienced in 1918, caused by a novel influenza subtype virus capable of causing severe respiratory disease and death. The avian influenza H5N1 virus, which has resulted in more than 250 human infections (*8*), has not acquired human influenza virus genes and lacks the ability to spread efficiently from human to human (*9*, *10*). Reassortment of avian H5N1 virus genes with human H3N2 influenza virus genes was shown to be insufficient for transmission of this avian virus (*11*), suggesting that additional unknown mutations are required for H5N1 to emerge as a pandemic strain.

The binding of influenza viruses to their target cells is mediated by the viral HA, which recognizes cell surface glycoconjugates containing terminal sialic acid (SA) residues. Avian influenza viruses preferentially bind SA linked to galactose by an α-2,3 linkage (α2,3 SA), which is found in high concentrations on the epithelial cells of the intestine of waterfowl and shorebirds (*12*). Conversely, human influenza viruses (H1 to H3 subtypes) more readily bind to receptors that contain terminal α-2,6-linked sialyl-galactosyl (α2,6 SA) moieties that are found on the human respiratory tract epithelium (*13*, *14*). The three influenza pandemic viruses of the last century, occurring in 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2), each possessed an HA with a human α2,6 SA binding preference and are thought to have originated from an avian virus possessing the α2,3 SA binding preference (*13*–*16*). It has been postulated that the lack of sustained human-to-human transmission of avian influenza H5N1 viruses is due to their α2,3 SA receptor binding preference (*17*–*19*). Higher proportions of α2,3 SA receptors in the human lower respiratory tract compared with the upper respiratory tract may explain the severity of H5N1 viral pneumonia in humans resulting from H5N1 viral attachment deep in the lungs (*17*, *19*).

Amino acids at positions 190 and 225 in the 1918 pandemic influenza virus HA determine its receptor binding specificity (*15*, *16*). In this study, we generated recombinant influenza viruses possessing all eight gene segments of the 1918 influenza virus to examine the role of receptor binding specificity on replication, pathogenicity, and transmissibility of this pandemic strain. We generated two variant A/South Carolina/1/18 (SC18) 1918 viruses in which the HA was altered to change the receptor binding specificity from the parental human α2,6 SA (SC18) receptor preference to an avian α2,3 SA receptor preference (AV18) or a mixed α2,6 and α2,3 SA specificity reflecting the A/New York/1/18 (NY18) virus binding specificity. The NY18 virus was a natural variant sequenced from an archived lung tissue sample prepared during autopsy of a patient who died within 6 days of hospitalization in September 1918 (*20*). The HA corresponding to NY18 virus was made by introducing a single amino acid substitution [Asp^{225}→Gly^{225} (D225G)] in the SC18 HA. The AV18 virus, which differs by one amino acid from NY18 virus, was made by introducing an additional amino acid change [Asp^{190}→Glu^{190} (D190E)] within the NY18 HA. Compared with the SC18 virus, the AV18 variant has two amino acid changes (D190E and D225G) in the HA, which matches the conserved avian consensus sequence in the receptor binding site and which converts it to the classic α2,3 SA receptor preference (*15*). A/Duck/Alberta/35/76 (Dk/Alb) and A/Texas/36/91 (Tx/91) viruses were included in the study as controls representative of an avian

Table 1. Titer of virus stocks prepared on MDCK cells with trypsin (1 μg/ml, Sigma) and incubated at 37°C with 5% CO_2 for 48 hours. Hemagglutination assay of viruses used 0.5% α-2,3-resialylated CRBCs, α-2,6-resialylated CRBCs, or untreated CRBCs. The results shown correspond to four hemagglutination units. Similar results were obtained when viruses were adjusted to 8, 16, or 32 hemagglutination units with untreated CRBCs.

	Amino acid position (H3 numbering)			Presence or absence of hemagglutination		
	190	225	Infectivity titer (pfu/ml)	α2,6 CRBCs	α2,3 CRBCs	Untreated CRBCs
SC18	D	D	4.8×10^7	+	−	+
NY18	D	G	3.3×10^7	+	+	+
AV18	E	G	5.0×10^7	−	+	+
Dk/Alb	E	G	2.2×10^7	−	+	+

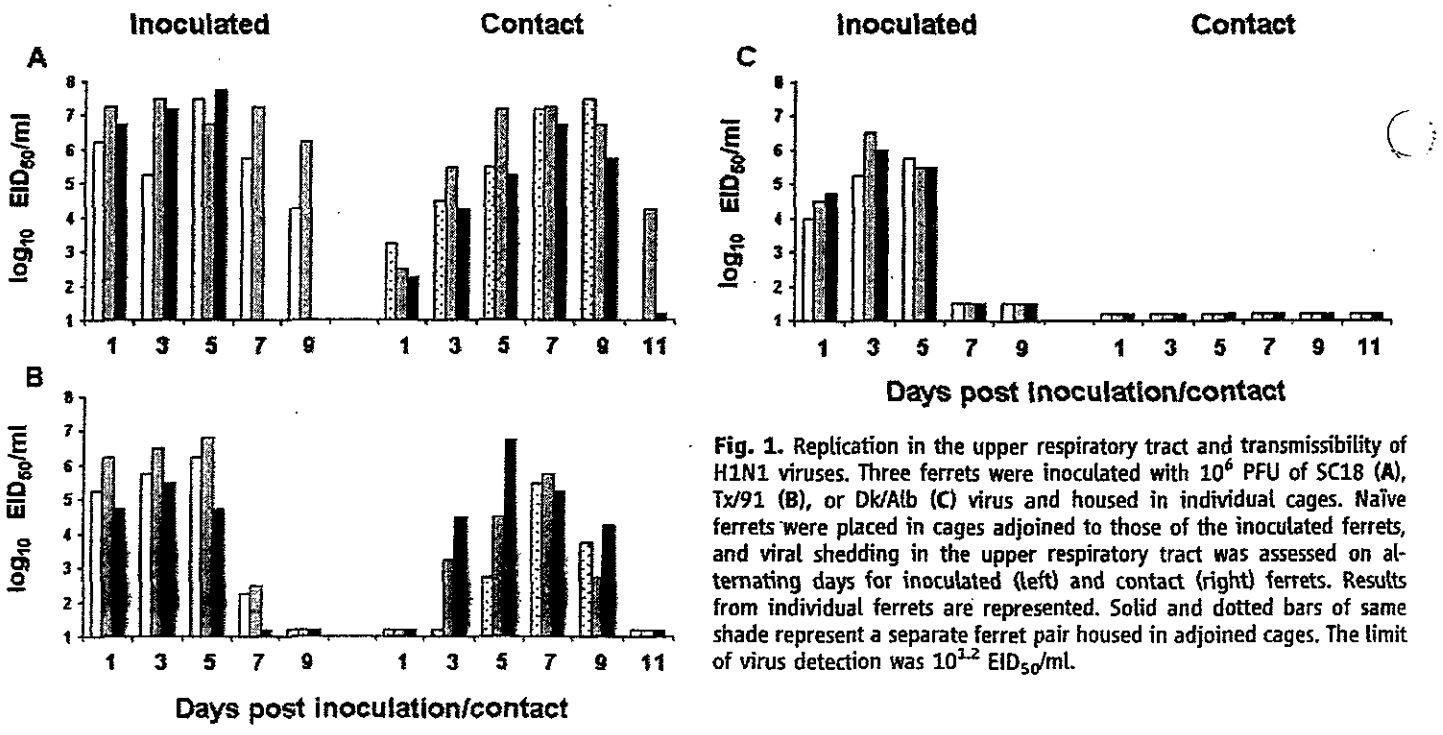

Fig. 1. Replication in the upper respiratory tract and transmissibility of H1N1 viruses. Three ferrets were inoculated with 10^6 PFU of SC18 (**A**), Tx/91 (**B**), or Dk/Alb (**C**) virus and housed in individual cages. Naïve ferrets were placed in cages adjoined to those of the inoculated ferrets, and viral shedding in the upper respiratory tract was assessed on alternating days for inoculated (left) and contact (right) ferrets. Results from individual ferrets are represented. Solid and dotted bars of same shade represent a separate ferret pair housed in adjoined cages. The limit of virus detection was $10^{1.2}$ EID_{50}/ml.

H1N1 virus and a human H1N1 virus, respectively. The 1918 viruses were generated by using the previously described reverse genetics system (*21–23*), and the identities of virus genes in the rescued viruses were confirmed by reverse transcription polymerase chain reaction and sequence analysis.

The rescued 1918 viruses containing the parental SC18 HA and the two variant HAs had similarly high infectivity titers in Madin-Darby canine kidney (MDCK) cells (Table 1). The receptor-binding properties of the 1918 viruses were confirmed in HA assays by using enzymatically modified chicken red blood cells (CRBCs) that contain either α2,3 or α2,6 SA, as previously described (*15*). The AV18 virus and the avian Dk/Alb control virus hemagglutinated the α2,3-resialylated CRBCs only, whereas the SC18 virus hemagglutinated the α2,6-resialylated CRBCs only. The NY18 virus hemagglutinated both α2,3- and α2,6-resialylated CRBCs.

Pathogenesis and transmissibility of the parental 1918 (SC18) virus were evaluated and compared with those of Tx/91 virus with an α2,6 SA receptor binding preference (*16*) and with those of the avian Dk/Alb virus possessing an α2,3 SA receptor binding preference (Table 1) (*24*). Ferrets were housed in adjacent cages that prevented direct and indirect contact between animals but allowed spread of influenza virus through the air (*11*, *25*). They were inoculated intranasally with 10^6 PFU (plaque forming units). One day after infection, three naïve ferrets housed in transmission cages were placed adjacent to each of the three inoculated ferrets (*26*). Three additional inoculated ferrets from each virus-infected group were killed on day 3 postinoculation (p.i.) for assessment of pathologic and virologic parameters (*26*). Ferrets inoculated with the parental SC18 virus shed high titers of infectious virus in nasal washes beginning as early as day 1 p.i. [50% egg infectious dose (EID_{50}/ml) from $10^{6.25}$ to $10^{7.25}$], and they sustained titers of $\geq 10^{4.5}$ EID_{50}/ml for 9 days p.i. (Fig. 1A, left). SC18 virus caused severe disease in all inoculated ferrets starting 2 days p.i.; symptoms included lethargy, anorexia, rhinorrhea, sneezing, severe weight loss (Table 2 and fig S1), and high fever, and two of the three animals died by day 11 p.i. Ferrets inoculated with H1N1 Tx/91 and Dk/Alb also shed high titers of virus in nasal washes (peak titers had EID_{50}/ml values from $10^{5.5}$ to $10^{6.8}$), but they were able to clear the virus from the upper respiratory tract by day 9 p.i. (Fig. 1, B and C) after displaying minimal symptoms (Table 2).

The human SC18 and Tx/91 viruses efficiently transmitted to each of the three contact ferrets (Fig. 1, A and B, right). The SC18 virus was detected in the contact ferrets as early as day 1 postcontact (p.c.), whereas the Tx/91 virus required 3 to 5 days to achieve detectable virus titers in nasal washes of the Tx/91 contact ferrets. The Tx/91 contact ferrets exhibited little morbidity, whereas all three SC18 contact ferrets exhibited severe signs of illness and weight loss, and one of three contact animals failed to clear the virus before it succumbed to infection on day 6 p.c. In contrast to the efficient spread of SC18 and Tx/91 viruses, the avian Dk/Alb virus was not transmitted to naïve contact ferrets, because virus was not detected in the nasal washes from the contact ferrets at any time. Furthermore, seroconversion was not detected by hemagglutination inhibition (HI) analysis of postexposure sera (Table 2). Both A/Duck/New York/15024/96 and A/Turkey/South Dakota/7034/86, which are representative avian viruses with an α2,3 SA receptor preference, exhibited efficient replication in the upper respiratory tract, but no transmission was detected between ferrets.

We introduced one– and two–amino acid substitutions into the 1918 virus HA to produce SC18 variants NY18 and AV18, respectively. A switch in receptor specificity from an α2,6 SA

Table 2. Clinical symptoms, virus replication, seroconversion, and transmissibility among ferrets inoculated with H1N1 viruses and among ferrets exposed to the inoculated animals (contacts). The percentage of mean maximum weight loss is shown. NW, nasal wash.

	Inoculated ferrets Number with characteristic/total number				Contact ferrets Number with characteristic/total number			Respiratory droplet transmission
	Sneezing (day of onset)	Weight loss (%)	Virus detected in NW	Seroconversion (range of HI antibody titer)	Weight loss (%)	Virus detected in NW	Seroconversion (range of HI antibody titer)	
SC18	3/3 (2)	3/3 (11.7)	3/3	1/1 (1280)*	2/3 (15.4)	3/3	3/3 (80–640)	Efficient
Tx/91	3/3 (2)	3/3 (6.2)	3/3	3/3 (160–640)	3/3 (3.5)	3/3	3/3 (160–320)	Efficient
Dk/Alb	2/3 (5)	2/3 (1.2)	3/3	3/3 (80–1280)	0/3	0/3	0/3	None
AV18	0/3	3/3 (14.7)	3/3	1/1 (640)*	0/3	0/3	0/3	None
NY18	0/3	3/3 (18.9)	3/3	2/2 (320–640)†	1/3 (1.4)	1/3	2/3 (40–80)	Inefficient

*Only one ferret survived and was tested. †Two ferrets survived and were tested.

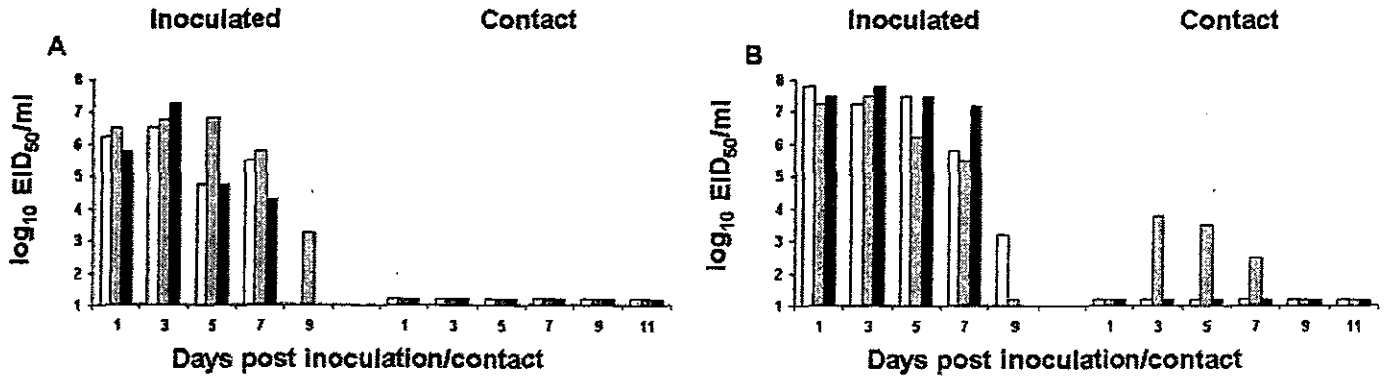

Fig. 2. Respiratory droplet transmissibility of 1918 viruses with mutated HA proteins. Three ferrets were inoculated with 10^6 PFU of AV18 (**A**) or NY18 (**B**) virus and placed in separate cages. Naïve ferrets were placed in cages adjoined to those of the inoculated ferrets, and viral shedding in the upper respiratory tract was assessed on alternating days for inoculated (left) and contact (right) ferrets. Results from individual ferrets are represented. Solid and dotted bars of same shade represent a separate ferret pair housed in adjoined cages.

(human) to an α2,3 SA (avian) binding preference abolished the transmissibility of the pandemic virus (Fig. 2 and Table 2). Although ferrets inoculated with AV18 virus exhibited severe illness (Table 2 and fig S1) and shed high titers of infectious virus in nasal washes (Fig. 2A, left), none of the three AV18 contact ferrets had detectable virus in nasal washes, and post-exposure sera collected from contact animals lacked antibodies against AV18. The NY18 virus, with dual α2,6 and α2,3 SA specificity, also resulted in severe illness and death among the inoculated ferrets, but it failed to transmit efficiently, as evidenced by the paucity of clinical symptoms and virus shedding among the contact ferrets (Fig. 2B). Two of the three NY18 contact ferrets seroconverted with relatively low HI titers of 40 and 80 (Table 2). The lack of efficient transmission was not due to the inability of the NY18 virus to replicate to high titers in the upper respiratory tract, including the nasal turbinates (Fig. 2B, left, and fig S2). Interestingly, no sneezing was noted among the AV18- and NY18-inoculated ferrets through a 14-day observation period, a finding consistent with the lack of notable sneezing observed in ferrets infected with H5N1 viruses (*11*).

Despite the differences in transmissibility of the parental 1918 (SC18) virus and the mutant 1918 viruses, similar damage to multiple lung lobes was observed 3 days after intranasal infection (*26*) (Fig. 3). Ferret lungs infected with SC18, AV18, and NY18 viruses exhibited necrotizing bronchiolitis and moderate to severe alveolitis with edema (Fig. 3, A to E, I, and J). Viral antigen was common in lung tissues, with localization in the upper to lower portions of the bronchial airways, bronchial and bronchiolar epithelium, and hyperplasic epithelium within alveoli (Fig. 3, F to H). Ferrets inoculated with control Tx/91 and Dk/Alb viruses generally showed a lack of significant lung lesions (Fig. 3, K to M).

Receptor binding, the initial event in influenza virus infection, was a major determinant of virus transmission efficiency of the H1N1 pandemic virus. This work also evaluates the virulence of the 1918 virus in a ferret model, a model that is believed to be more representative than the mouse model of disease caused by influenza viruses in humans. In contrast to other human influenza virus strains, the 1918 virus demonstrated uniquely high virulence and lethality in ferrets. The mutant 1918 virus possessing α2,3 SA receptor binding (AV18) was equally virulent in ferrets as the parental SC18 strain at the dose administered. Remarkably, the AV18 virus replicated in the upper respiratory tract as efficiently as the parental SC18 virus, but it failed to transmit to contact ferrets. Moreover, a human α2,6 SA binding preference is essential for optimal transmission of this exceptionally virulent virus. The introduction of a single mutation that converts the HA to dual α2,6 and α2,3 SA binding specificity (NY18) reduced the high transmissibility observed with the parental 1918 (SC18) virus. This result is consistent with the previously demonstrated lack of transmissibility of an H5N1 2003 virus that possessed dual α2,6 and α2,3 SA specificity due to a naturally acquired mutation at HA residue 223 (H5 numbering; residue 227 by H3 numbering) (*11*, *27*).

Our findings raise the possibility that, to become more transmissible, the currently circulating avian influenza H5N1 virus may require a receptor binding change to a predominant α2,6 SA binding preference. Such a modification of H5 HA may result in improved virus binding to

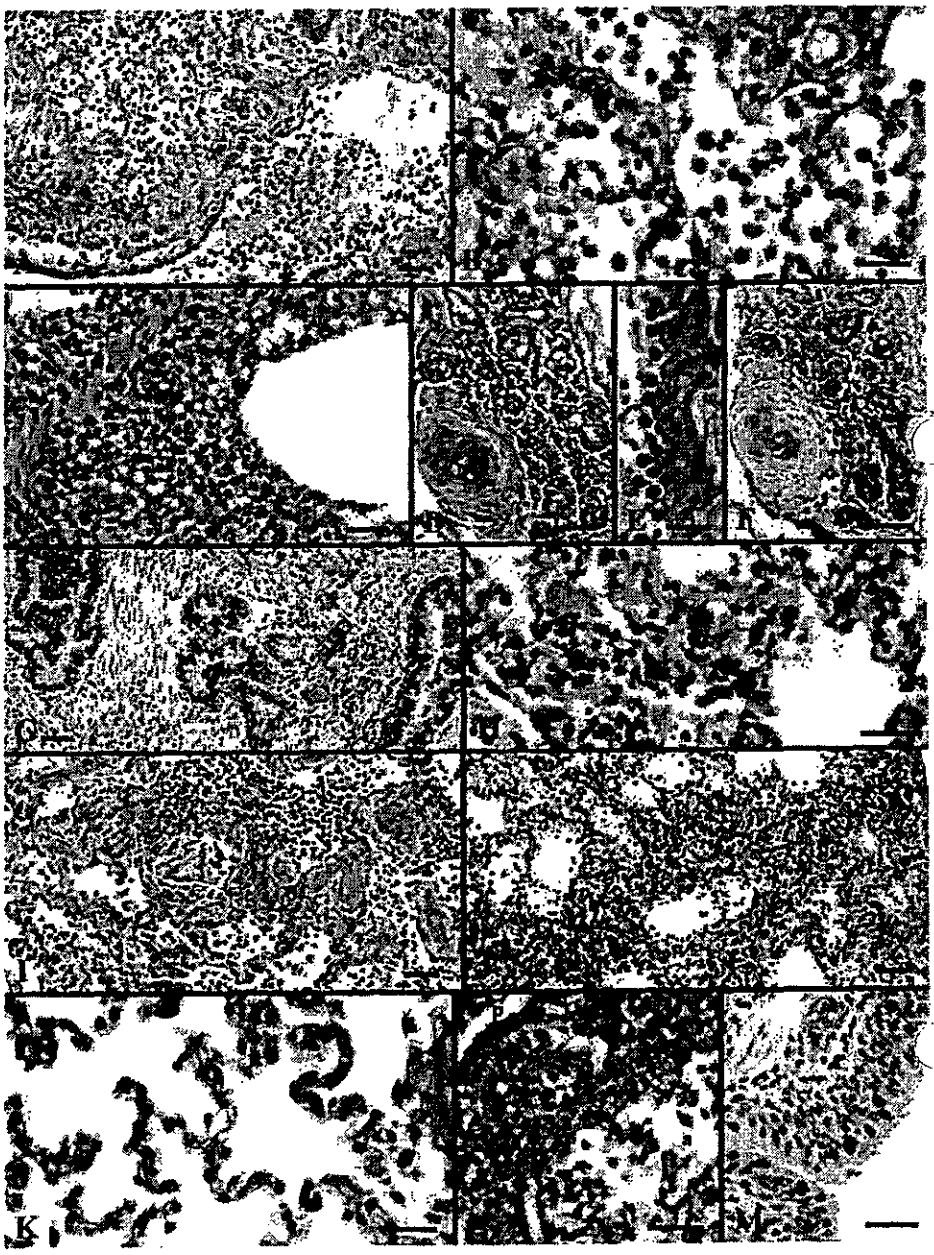

Fig. 3. Photomicrographs of hematoxylin and eosin [(A) to (E) and (I) to (L)] and immunohistochemically [(F) to (H) and (M)] stained lung sections from influenza virus–infected ferrets sampled on day 3 after inoculation. (**A to H**) Lung sections infected by SC18 virus. (A) Severe necrotizing bronchiolitis with severe diffuse alveolitis and edema. Scale bar indicates 50 μm. (B) Severe diffuse alveolitis; scale bar, 20 μm. (C) Necrotizing bronchiolitis; scale bar, 30 μm. (D) Necrosis and (F) associated influenza viral antigen in submucosal serous glandular epithelium of a bronchus; scale bar, 50 μm. (E) Margination and adhesion of neutrophils to endothelial cells of a pulmonary arteriole; scale bar, 20 μm. (G) Influenza viral antigen in epithelium of a primary bronchiole; scale bar, 50 μm. (H) Viral antigen commonly in macrophages and alveolar epithelial cells; scale bar, 20 μm. (I) NY18 virus; severe diffuse alveolitis with accompanying necrotizing bronchiolitis; scale bar, 50 μm. (J) AV18 virus; diffuse severe alveolitis and edema with necrotizing bronchiolitis; scale bar, 50 μm. (K) Tx/91 virus; normal alveoli; scale bar, 15 μm. (L) Dk/Alb virus, purulent bronchiolitis (p) with peribronchiolar mixed cell inflammation and associated moderate alveolitis (a); scale bar, 50 μm. (M) Dk/Alb viral antigen in bronchial epithelium; scale bar, 30 μm.

human tracheal epithelial cells expressing high amounts of terminal α2,6 SA motifs and, simultaneously, in an improved ability to overcome the inhibitory effects of human bronchial mucins associated with α2,3 SA receptors (*28*). However, mutations that caused a shift from the avian-type to human-type receptor binding specificity for the H1 subtype do not cause an equivalent shift in specificity for the H5 subtype (*24*). Likewise, the amino acid changes required to alter the H3 HA from an avian- to human-type receptor binding specificity are different from those required for the H1 HA. Therefore, it is likely that different avian HA subtypes have different structural requirements to confer receptor specificity. Thus, it is currently unknown which additional mutations in the H5 HA would cause a shift to the human-type specificity, which may be required for H5N1 viruses to transmit efficiently among humans.

References and Notes

1. W. H. Frost, *Public Health Rep.* 35, 584 (1920).
2. F. Burnet, E. Clark, *Influenza: A Survey of the Last 50 Years in the Light of Modern Work on the Virus of Epidemic Influenza* (MacMillan, Melbourne, 1942).
3. T. M. Tumpey *et al.*, *Science* 310, 77 (2005).
4. J. C. Kash *et al.*, *Nature* 443, 578 (2006).
5. D. Kobasa *et al.*, *Nature* 431, 703 (2004).
6. K. D. Patterson, G. F. Pyle, *Bull. Hist. Med.* 65, 4 (1991).
7. C. Viboud *et al.*, *Vaccine* 24, 6701 (2006).
8. World Health Organization, "Epidemic and pandemic alert and response (EPR): Avian influenza" (available at www.who.int/csr/disease/avian_influenza/en/index.html).
9. C. B. Bridges *et al.*, *J. Infect. Dis.* 185, 1005 (2002).
10. J. M. Katz *et al.*, *J. Infect. Dis.* 180, 1763 (1999).
11. T. R. Maines *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 103, 12121 (2006).
12. T. Ito *et al.*, *J. Virol.* 72, 7367 (1998).
13. M. Matrosovich *et al.*, *J. Virol.* 74, 8502 (2000).
14. R. J. Connor *et al.*, *Virology* 205, 17 (1994).
15. L. Glaser *et al.*, *J. Virol.* 79, 11533 (2005).
16. J. Stevens *et al.*, *J. Mol. Biol.* 355, 1143 (2006).
17. K. Shinya *et al.*, *Nature* 440, 435 (2006).
18. M. Matrosovich, N. Zhou, Y. Kawaoka, R. Webster, *J. Virol.* 73, 1146 (1999).
19. D. van Riel *et al.*, *Science* 312, 399 (2006); published online 22 March 2006 (10.1126/science.1125548).
20. A. H. Reid, T. G. Fanning, J. V. Hultin, J. K. Taubenberger, *Proc. Natl. Acad. Sci. U.S.A.* 96, 1651 (1999).
21. E. Fodor *et al.*, *J. Virol.* 73, 9679 (1999).
22. C. F. Basler *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 98, 2746 (2001).
23. The 1918 viruses were handled under biosafety level 3 enhanced (BSL3) containment in accordance with guidelines of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) (available at www.cdc.gov/flu/h2n2bsl3.htm) and in accordance with requirements of the U.S. Department of Agriculture (USDA)–CDC select agent program.
24. J. Stevens *et al.*, *Science* 312, 404 (2006); published online 15 March 2006 (10.1126/science.1124513).
25. The use of the term "respiratory droplet transmission" throughout this report refers to transmission in the absence of direct or indirect contact and does not imply an understanding of the droplet size involved in virus spread between ferrets. The ability of each virus to undergo respiratory droplet transmission among ferrets was assessed by measuring virus titers in nasal washes from contact animals every other day for 9 days. HI analysis was also performed on postexposure ferret sera collected 18 days p.c. Although only single experiments are reported, there was little variation in the replication and transmissibility among the three inoculated and the three contact ferrets for each of the seven H1N1 viruses tested in this study.
26. Material and methods are available on *Science* Online.
27. A. Gambaryan *et al.*, *Virology* 344, 432 (2006).
28. G. Lamblin *et al.*, *Glycoconj. J.* 18, 661 (2001).

29. We thank C. Chesley for critical review of the manuscript and J. Beck for technical assistance. This work was partially supported by NIH grant PO1 AI058113 (to A.G.-S.), the Northeast Biodefense Center (U54 AI057158), and the Center for Investigating Viral Immunity and Antagonism (CIVIA) (U19 AI62623). Work in the A.G.-S. and P.P. laboratories is partially supported by the W. M. Keck Foundation. P.P. is a Senior Scholar of the Ellison Medical Foundation. This work was partially supported by Agriculture Research Service, USDA, Current Research Information System project number 6612-32000-039-00D.

Supporting Online Material

www.sciencemag.org/cgi/content/full/315/5812/655/DC1
Materials and Methods
SOM Text
Figs. S1 and S2
References

12 October 2006; accepted 13 December 2006
10.1126/science.1136212

Protein Kinase C β and Prolyl Isomerase 1 Regulate Mitochondrial Effects of the Life-Span Determinant p66^{Shc}

Paolo Pinton,[1,2*] Alessandro Rimessi,[1,2*] Saverio Marchi,[1,2] Francesca Orsini,[3,4] Enrica Migliaccio,[3,4] Marco Giorgio,[3,4] Cristina Contursi,[5] Saverio Minucci,[5] Fiamma Mantovani,[6,7] Mariusz R. Wieckowski,[1,2,8] Giannino Del Sal,[6,7] Pier Giuseppe Pelicci,[3,4,9] Rosario Rizzuto[1,2]†

66-kilodalton isoform of the growth factor adapter Shc (p66^{Shc}) translates oxidative damage into cell death by acting as reactive oxygen species (ROS) producer within mitochondria. However, the signaling link between cellular stress and mitochondrial proapoptotic activity of p66^{Shc} was not known. We demonstrate that protein kinase C β, activated by oxidative conditions in the cell, induces phosphorylation of p66^{Shc} and triggers mitochondrial accumulation of the protein after it is recognized by the prolyl isomerase Pin1. Once imported, p66^{Shc} causes alterations of mitochondrial Ca^{2+} responses and three-dimensional structure, thus inducing apoptosis. These data identify a signaling route that activates an apoptotic inducer shortening the life span and could be a potential target of pharmacological approaches to inhibit aging.

The protein p66^{Shc} (*1*–*4*) is an alternatively spliced isoform of a growth factor adapter that is phosphorylated upon oxidative stress (*2*). Ablation of the p66^{Shc} gene causes life-span prolongation with no pathological consequence (*2*). A fraction of p66^{Shc} localizes to mitochondria (*3*–*5*), where it binds to cytochrome c and acts as oxidoreductase, generating reactive oxygen species (ROS) and leading to organelle dysfunction and cell death (*5*). The route leading to p66^{Shc} activation is still unclear. Phosphorylation of a critical serine (Ser^{36}) is necessary (*2*), but the kinase responsible has not been identified. Moreover, mitochondrial p66^{Shc} is unphosphorylated, indicating that additional regulatory elements must exist.

Mitochondria receive, under stimulation by physiological agonists or toxic agents, Ca^{2+}-mediated inputs (*6*–*8*) that are decoded into effects as diverse as metabolic stimulation and apoptosis (*9*). Ca^{2+} responsiveness is a highly sensitive readout of mitochondrial state: Partial defects in mitochondrial energization, as in mitochondrial diseases, cause defects in Ca^{2+} handling by the organelle (*10*). Moreover, mitochondrial Ca^{2+} uptake is modulated by regulatory proteins such as kinases. Some protein kinase C (PKC) isoforms (*11*) specifically affect the responses of mitochondrial Ca^{2+} to agonists (PKCβ reduces them, whereas PKCζ enhances them) (*12*). PKCs are also proposed to be activated in conditions of oxidative stress (*13*). We therefore used aequorin to monitor cellular concentrations of Ca^{2+}, a green fluorescent protein with mitochondrial presequence (mtGFP) to monitor organelle structure, and other molecular tools to clarify the signaling route linking the oxidative challenge to the activation of p66^{Shc} proapoptotic effect within

[1]Department of Experimental and Diagnostic Medicine, Section of General Pathology and Interdisciplinary Center for the Study of Inflammation (ICSI), University of Ferrara, Ferrera, Italy. [2]Emilia Romagna Laboratory for Genomics and Biotechnology (ER-Gentech), University of Ferrara, Ferrera, Italy. [3]Department of Experimental Oncology, European Institute of Oncology, Milan, Italy. [4]Fondazione Italiana per la Ricerca sul Cancro (FIRC) Institute of Molecular Oncology, Milan, Italy. [5]Congenia s.r.l., Milan, Italy. [6]Laboratorio Nazionale, Consorzio Interuniversitario per le Biotecnologie, Area Science Park, Trieste, Italy. [7]Department of Biochimica Biofisica Chimica delle Macromolecole, University of Trieste, Italy. [8]Department of Cellular Biochemistry, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Poland. [9]Department of Medicine and Surgery, University of Milan, Italy.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: r.rizzuto@unife.it

別紙様式第2-1

No. 25

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2007. 2. 19	該当なし	

一般的名称	乾燥濃縮人血液凝固第Ⅷ因子	研究報告の公表状況	Canadian Blood Services Web Site. Available from: URL: http://www.bloodservices.ca/centreapps/internet/uw_v502_mainengine.nsf/9749ca80b75a038585256aa20060d703/5c76eaee1de6518b852572420076488e?OpenDocument	公表国
販売名(企業名)	クロスエイトM250(日本赤十字社) クロスエイトM500(日本赤十字社) クロスエイトM1000(日本赤十字社)			カナダ

研究報告の概要

○問診票改訂 2006年12月18日
2006年12月18日付で、カナダ血液サービスは供血者が供血前に記入する供血記録の問診事項に一部修正を加える。
カナダ保健局の指示により、カナダ血液サービスは、ヒト以外の霊長類(サル、ヒヒ、チンパンジー、マカク、あるいはその血液や唾液など)との職業的接触に関する質問「あなたは過去のあるいは現在の仕事上サルやその体液を取り扱ったことがありますか?」を追加した。
サル泡沫状ウイルス(SFV)に関する認可された標準検査法がないため、供血者がこの質問に「はい」と答えた場合は無期限に供血延期となる。研究所で霊長類を扱う人、獣医師、動物園職員などが延期対象となるだろう。
SFVはサルやヒトにおけるいかなる疾患や健康被害とも関連していないが、最近の研究では、将来疾患や健康被害を引き起こす可能性を否定できないとされている。そのため、予防的措置としてこの質問が付け加えられた。

157

使用上の注意記載状況・その他参考事項等

クロスエイトM250
クロスエイトM500
クロスエイトM1000

血液を原料とすることに由来する感染症伝播等
vCJD等の伝播のリスク

報告企業の意見	今後の対応
カナダ血液サービスは、供血時の問診にヒト以外の霊長類との職業的接触に関する質問を追加したとの報告である。	SFVはレトロウイルスに属する脂質膜を持つRNAウイルスである。これまで、本製剤によるSFV感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されていると考えるが、念のため今後も情報収集に努める。なお、日本赤十字社では帰国後4週間は献血不適とし、輸入感染症の防止に努めている。

8

Changes to the Donor Questionnaire

December 18, 2006

As of December 18th, 2006 Canadian Blood Services is making some adjustments to questions in the Record of Donation that blood donors complete prior to giving blood.

At the direction of Health Canada, Canadian Blood Services is adding a question regarding occupational contact with non-human primates such as monkeys, baboons, chimpanzees or macaques or their blood or saliva: "Have you, in your past or present job, taken care of or handled monkeys or their body fluids?"

Since there is no approved standard test for Simian foamy virus (SFV), donors who respond positively to the question will be deferred indefinitely. People who could be deferred include handlers of non-human primates in lab settings, veterinarians or zoo workers.

Although SFV has not been associated with any disease or health conditions in monkeys or humans, current research does not allow us to rule out the possibility that this virus could result in future disease or health conditions. So this question is being added as a precautionary measure.

As well Canadian Blood Services is removing or altering three additional questions on the record of donation:

- The question " In the past week, have you had a fever with headache?" is being eliminated. This question was added after an FDA recommendation about West Nile Virus. A positive response meant the donor would be deferred. However evidence suggests this question is no longer considered to be useful and is also being removed by U.S. blood operators and Héma-Quebec. (Question 3)
- The phrase "sometimes used for treatment of infertility or to promote weight loss" is being removed from the question " Have you ever taken human pituitary growth hormones, human pituitary gonadotrophin hormone." This hormone is no longer used in those treatments. (Question 7 b)
- The list of specific illnesses in Question 8 is repetitive of other questions on the form. So Canadian Blood Services is removing references to "liver problems," "convulsions," "blood pressure problems," "heart surgery," and "ulcerative colitis."

Back to *Speeches & Public Statements* >>

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 2007年2月2日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	フィブリノゲン加第XIII因子		研究報告の公表状況	Rift Valley Fever Outbreak --- Kenya, November 2006--January 2007	公表国 米国	
販売名（企業名）	ボルヒール					

研究報告の概要	使用上の注意記載状況・その他参考事項等
（問題点：ケニアにおいてリフトバレー熱がアウトブレイクし、1月25日現在、404症例（死亡118症例）が確認されている。） 2006年12月中旬に、ケニア保健省に発熱および全身性の出血に関連した原因不明の死亡がNorth Eastern州に位置するGarissa地区から複数報告され、12月20日までに合計11例の死亡が報告された。最初の患者19例から収集した血清サンプルのうちの10例からリフトバレー（RFV）ウイルスRNAまたはRFVウイルスに対するIgM抗体が発見された。ヒトへのRVFウイルス感染は、RVFウイルス感染した動物を餌とした蚊や蚊以外の節足動物に刺されたり、ウイルス血症を有す動物、特に家畜に接触したりして起こる。North Eastern州では、家畜の死亡や原因不明な動物の流産といった報告があり、このこともRVFアウトブレイクを裏付けている。 アウトブレイクは複数の州および地区に拡大し、1月25日現在、症例404例（死亡118例）が確認されているが、アウトブレイクは2006年12月24日にピークを迎え、2006年12月27日以降、一日の症例数は減少傾向にある。12月27日付けでガリッサ地区における家畜のと殺が禁止され、その他の地区でもRVFが検出されたことから、その禁止は拡大された。2007年1月8日には弱毒生RVFワクチン接種が始まった。	記載なし

報告企業の意見	今後の対応
別紙のとおり	今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

19