Title	H5N1 virus resistant to antiviral drug
Author(s)	Chen, H; Guan, Y
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HL Chen *, Y Guan

KEY MESSAGES

1. This study investigated the geographical distribution and growth properties of avian influenza A (H5N1) isolates with mutations that confer resistance to amantadine and rimantadine. It also explored whether naturally occurring mutations associated with resistance to oseltamivir are present at a low frequency in H5N1 isolates and if so, whether these quasi-species may be the source of the emergence of oseltamivir-resistant strains following exposure to this drug.
2. Naturally occurring avian H5N1 virus mutants resistant to the main types of antiviral drugs were noted.
3. The fitness of these mutants in avian and mammalian hosts needs further investigation.

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HL Chen *, Y Guan

Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong

* Principal applicant and corresponding author: hlchen@hku.hk

Avian influenza A (H5N1) virus is common in poultry and has caused sporadic human infections since 2003. Antiviral drugs are essential to contain and delay the spread of the virus. Nonetheless, resistance to the M2 ion channel blockers, amantadine and rimantadine, and the neuraminidase inhibitor—oseltamivir—have been detected in H5N1 virus.

Human infections with H5N1 virus were first documented in Hong Kong in 1997 and then in China in 2003. More than 500 human infections have been identified in 15 countries; over 50% of cases are fatal.[1]

Currently available anti-influenza drugs (adamantanes, amantadine, and rimantadine) block the ion channel formed by the M2 protein of the influenza virus, as well as the neuraminidase inhibitors—oseltamivir and zanamivir.[2]

Resistance to amantadine and rimantadine has been detected in human influenza viruses, including the pandemic (H1N1) 2009 virus,[3] and in avian H5N1 viruses isolated in Vietnam and Thailand in 2004 and 2005.[4] Stockpiling of neuraminidase inhibitors, in particular oseltamivir, is recommended by the World Health Organization in response to a potential pandemic. The efficacy of oseltamivir in the treatment of H5N1 infection is not clear, and resistant variants have been identified in H5N1 human cases treated with oseltamivir.[1] Emergence of resistance to oseltamivir in seasonal H1N1 virus since 2007 suggests that the resistance mutation—His274Tyr—may occur naturally.[5] This study aimed to investigate whether resistance to amantadine is also prevalent in H5N1 viruses, and whether mutations associated with oseltamivir resistance occur in avian H5N1 viruses.

Resistance to amantadine and rimantadine is mainly found in H5N1 viruses circulating in Vietnam and Thailand during 2004 and 2005 (data not shown). The dual Leu26Ile and Ser31Asn mutations in the M2 gene are responsible for this resistance. In vitro, the dual Leu26Ile and Ser31Asn mutations confer a growth advantage to the H5N1 virus, especially at 40°C. This suggests a possible mechanism for the expansion of mutant viruses in poultry that have a higher body temperature than humans (Fig). Resistance to adamantanes is much less prevalent in H5N1 viruses circulating in Indonesia, the Middle East, and China. This suggests that these drugs may still have prophylactic and therapeutic value for the H5N1 virus.

Resistance to the neuraminidase inhibitor—oseltamivir—has been found in H5N1 viruses. It is not clear whether the mutation—His274Tyr—originated in patients during treatment or whether it is derived from an avian source. In 2002, a H5N1 isolate was found to contain the His274Tyr mutation and was resistant to oseltamivir. His274Tyr quasi-species in H5N1 virus isolates were examined to investigate whether the His274Tyr mutant virus might naturally occur at low levels mixed with wild type virus in H5N1 poultry infections (data not shown). The His274Tyr quasi-species were more frequently found in isolates from infected chickens than from other ducks and geese, but no geographical difference was noted. His274Tyr mutant H5N1 viruses exhibited host specificity. A distinctive interaction between the HA and the NA proteins in some H5N1 isolates may also result in reduced susceptibility to oseltamivir. The mechanism for the emergence of the dominant His274Tyr in H1N1 virus was investigated to understand the fitness of the NA gene in N1 subtype viruses.

Although vaccination is a principal defence against influenza, rapid vaccine development during a pandemic is challenging. Antiviral drugs play an essential role in the control of an outbreak, delaying virus spread, as well as preventing and treating disease. A clear profile of H5N1 resistance to anti-influenza drugs is not available, as studies are still in the animal phase.

Although amantadine-resistant viruses have been found in Asia, their distribution was geographically and temporally confined to Thailand, Vietnam, and Cambodia; most isolates from other places are sensitive to amantadine, as have been most avian H5N1 viruses detected since 2006. This apparent geographical disparity in the susceptibility of H5N1 isolates to amantadine is unknown. The distinct and conserved pattern of the paired Leu26Ile and Ser31Asn mutations suggests that the Thai, Vietnamese, and Cambodian viruses originated from a single virus introduced into or generated within the region. Dual Leu26Ile and Ser31Asn mutations are rare among other influenza A viruses. The high incidence of 26Ile and its exclusive association with 31Asn in H5N1 isolates suggest that viruses carrying the dual mutation were stably selected; no single 26Ile variants were detected.

Neuraminidase inhibitors are the first-line antivirals for a pandemic. Resistance to oseltamivir has been reported in human H5N1 isolates. Oseltamivir-resistant strains bearing the His274Tyr mutation are present at low levels within some H5N1 virus populations. Isolation of one resistant mutant strain from an infected chicken suggests that such naturally occurring mutants may become the main population if they gain growth fitness in the host. This assertion is supported by the spread of a seasonal H1N1 virus carrying the His274Tyr oseltamivir-resistance mutation since 2007. Naturally occurring His274Tyr mutations in the 2009 H1N1 virus were also characterised. It is important to closely survey genetic mutations associated with resistance to neuraminidase inhibitors in influenza A viruses, and to study the replication fitness of resistant variants.

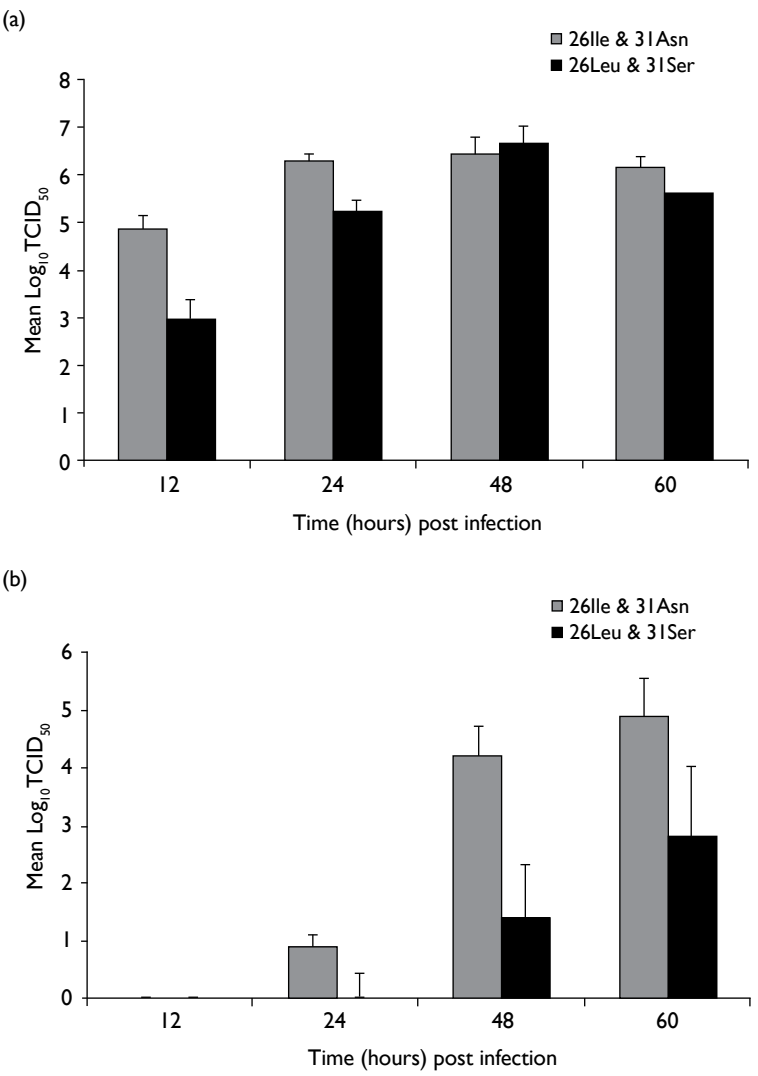

FIG. Growth properties of amantadine-resistant variant in MDCK cells H5N1 virus strain A/Vietnam/1194/04 (26Ile & 31Asn in M2 gene and resistant to amantadine) and a recombinant version of the same virus (26Leu & 31Ser in M2 gene and susceptible to amantadine) for growth kinetics in MDCK cells cultured at (a) 37°C and (b) 40°C

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