11 May 2010

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News – Pandemic Influenza Edition #111

1. A LOW OXYGEN CONSUMPTION PNEUMATIC VENTILATOR FOR EMERGENCY CONSTRUCTION DURING A RESPIRATORY FAILURE PANDEMIC: *"Such a device could be mass-produced for crises characterised by an overwhelming demand for mechanical ventilation and a limited oxygen supply."*

2. ROLE OF SECONDARY SIALIC ACID BINDING SITES IN INFLUENZA N1 NEURAMINIDASE: *"Our results indicate possible lowered HA activity for this secondary sialic acid site. which may be an important event in the emergence of the current pandemic strain."*

3. DYNAMICS OF INFLUENZA VIRUS INFECTION AND PATHOLOGY: *"We then explore how differences in the influence of viral proteins on interferon kinetics can account for the observed spectrum of virus shedding, immune response, and influenza pathology."*

4. MIXED INFECTIONS OF PANDEMIC H1N1 AND SEASONAL H3N2 VIRUSES IN 1 OUTBREAK: *"Therefore, competitive circulation of seasonal influenza A virus with the pandemic H1N1 virus seems less likely."*

5. MIXED LINEAGE KINASE 3 DEFICIENCY DELAYS VIRAL CLEARANCE IN THE LUNG AND IS ASSOCIATED WITH DIMINISHED INFLUENZA-INDUCED CYTOPATHIC EFFECT IN INFECTED CELLS: *"These findings support a role for MLK3 in viral production during influenza infection."*

6. KILLING OF AVIAN AND SWINE INFLUENZA VIRUS BY NATURAL KILLER CELLS: *"However, importantly, while the swine H1-NKp46 interactions lead to the direct killing of the infected cells, the H5-NKp46 interactions were unable to elicit direct killing, probably because the NKp46 binding sites for these two viruses are different."*

7. IDENTIFICATION OF BROAD BINDING CLASS I HLA SUPERTYPE EPITOPES TO PROVIDE UNIVERSAL COVERAGE OF INFLUENZA A VIRUS: *"Accordingly, 28 different epitopes antigenic for human donor PBMC were identified and 25 were 100% conserved in the newly emerged swine-origin H1N1 strain."*

8. FLU VIRUS TRANSPORTED BY DUST STORMS: *"The finding might explain why not all outbreaks of bird flu in animals have been linked to movement of poultry or wild birds, the authors say."*

CB Daily Report

Chem-Bio News

A LOW OXYGEN CONSUMPTION PNEUMATIC VENTILATOR FOR EMERGENCY CONSTRUCTION DURING A RESPIRATORY FAILURE PANDEMIC
Health & Medicine Week
April 26, 2010

"The UK influenza pandemic plan predicts up to 750,000 additional deaths with hospitals prioritising

patients against inadequate resources. We investigated three prototype low-cost, gas-efficient, pneumatic ventilators in a test lung model at different compliance and rate settings.”

"Mean (SD) oxygen consumption was 0.913 (0.198) and 1.119 (0.267) l.min(-1) at tidal volumes of 500 ml and 700 ml respectively. Values of F(I)o(2) increased marginally as lung compliance reduced, reflecting the increased ventilator workload and consequent increased enrichment of breathing gas by waste oxygen from the pneumatic mechanism. We also demonstrated that a stable nitric oxide concentration could be delivered by this design following volumetric principles. It is possible to make a gas-efficient ventilator costing less than 200 pounds from industrial components for use where oxygen is available at 2-4 bar, with no pressurised air or electrical requirements.”

"Such a device could be mass-produced for crises characterised by an overwhelming demand for mechanical ventilation and a limited oxygen supply."

The full article can be found at: (D. Williams, et. al., “A low oxygen consumption pneumatic ventilator for emergency construction during a respiratory failure pandemic.” Anaesthesia, 2010;65(3):235-42). Link not available.
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ROLE OF SECONDARY SIALIC ACID BINDING SITES IN INFLUENZA N1 NEURAMINIDASE
Health & Medicine Week
April 19, 2010

"Within influenza viral particles, the intricate balance between host cell binding and sialic acid receptor destruction is carefully maintained by the hemagglutinin (HA) and neuraminidase (NA) glycoproteins, respectively. A major outstanding question in influenza biology is the function of a secondary sialic acid binding site on the NA enzyme."

"Through a series of Brownian dynamics (BD) simulations of the avian N1, human pandemic N2, and currently circulating pandemic (H1)N1 enzymes, we have probed the role of this secondary sialic acid binding site in the avian N1 subtype. Our results suggest that electrostatic interactions at the secondary and primary sites in avian NA may play a key role in the recognition process of the sialic acid receptors and catalytic efficiency of NA. This secondary site appears to facilitate the formation of complexes with the NA protein and the sialic acid receptors, as well as provide HA activity to a lesser extent. Moreover, this site is able to steer inhibitor binding as well, albeit with reduced capacity in N1, and may have potential implications for drug resistance of optimal inhibitor design. Although the secondary sialic acid binding site has previously been shown to be nonconserved in swine NA strains, our investigations of the currently circulating pandemic H1N1 strain of swine origin appears to have retained some of the key features Of the Secondary sialic acid binding site.”

"Our results indicate possible lowered HA activity for this secondary sialic acid site. which may be an important event in the emergence of the current pandemic strain."

The full article can be found at: (J.C. Sung, et. al., “Role of Secondary Sialic Acid Binding Sites in Influenza N1 Neuraminidase”. Journal of the American Chemical Society, 2010;132(9):2883+). Link not available.
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DYNAMICS OF INFLUENZA VIRUS INFECTION AND PATHOLOGY
Drug Week
April 30, 2010

"A key question in pandemic influenza is the relative roles of innate immunity and target cell depletion in limiting primary infection and modulating pathology. Here, we model these interactions using detailed data from equine influenza virus infection, combining viral and immune (type I interferon) kinetics with estimates of cell depletion."

"The resulting dynamics indicate a powerful role for innate immunity in controlling the rapid peak in virus shedding. As a corollary, cells are much less depleted than suggested by a model of human influenza based only on virus-shedding data. We then explore how differences in the influence of viral proteins on interferon kinetics can account for the observed spectrum of virus shedding, immune response, and influenza pathology."

The full article can be found at: (R.A. Saenz, et. al., "Dynamics of influenza virus infection and pathology". Journal of Virology, 2010;84(8):3974-83). Link not available.
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MIXED INFECTIONS OF PANDEMIC H1N1 AND SEASONAL H3N2 VIRUSES IN 1 OUTBREAK
Medical Letter on the CDC & FDA
May 9, 2010

"In early September 2009, an outbreak of influenza occurred at a college campus in Beijing, China, in which both pandemic H1N1 and seasonal H3N2 viruses were detected."

"Epidemiologic, clinical data were collected by interviewing patients and retrieving medical records. Individual contact tracing was performed for detailed contact information. Viruses were identified by reverse-transcription polymerase chain reaction assays followed by sequence analysis. The hemagglutination inhibition test was used to detect antibodies to both viruses for paired serum samples. Forty of 45 people with influenza-like illness had laboratory-confirmed influenza A infection; 22 of these 40 people were infected with pandemic H1N1 virus, 12 were infected with seasonal H3N2 virus, and 6 were coinfected with both viruses. In the subsequent generation of cases with mixed infection, we detected pandemic H1N1 virus infection more often than seasonal H3N2 virus infection. The clinical patterns were essentially similar for patients with different virus infections. No substantial differences in sequences were observed in either pandemic H1N1 or seasonal H3N2 virus between patients with mixed and single infection. Sequence analyses revealed that all of the detected viruses were susceptible to oseltamivir but resistant to adamantane. Hemagglutination inhibition tests of paired serum samples confirmed mixed infection in the outbreak. Cocirculation of pandemic H1N1 virus and seasonal H3N2 virus led to a mixed infection in patients. Pandemic H1N1 virus, however, took prevalence over seasonal influenza virus in the course of transmission."

"Therefore, competitive circulation of seasonal influenza A virus with the pandemic H1N1 virus seems less likely."

The full article can be found at: (W. Liu, et. al., "Mixed infections of pandemic H1N1 and seasonal H3N2 viruses in 1 outbreak". Clinical Infectious Diseases, 2010;50(10):1359-65). Link not available.
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MIXED LINEAGE KINASE 3 DEFICIENCY DELAYS VIRAL CLEARANCE IN THE LUNG AND IS ASSOCIATED WITH DIMINISHED INFLUENZA-INDUCED CYTOPATHIC EFFECT IN INFECTED CELLS
Health & Medicine Week
April 26, 2010

"One particular pathway, the c-Jun amino-terminal kinase (JNK) cascade is activated following influenza infection and blocking JNK leads to enhanced viral replication. We hypothesize that Mixed Lineage Kinase 3 (MLK3), an upstream regulator of JNK, is involved in the host response to influenza. To test this, wild-type and MLK3-/-mice were infected with pathogenic strain of influenza A virus, A/PR/8/34 (PR8). Although, cellular and humoral immune responses were similar between wild-type and MLK3-/-hosts, the viral load in the lungs was comparatively higher in MLK3-/-mice at day 8 post-infection. Consistent with this, MLK3-/-murine lung fibroblast and epithelial cells had prolonged survival and increased virion production following infection compared to wild-type."

"These findings support a role for MLK3 in viral production during influenza infection."

The full article can be found at: (E.A. Desmet, et. al., “Mixed Lineage Kinase 3 deficiency delays viral clearance in the lung and is associated with diminished influenza-induced cytopathic effect in infected cells”. Virology, 2010;400(2):224-32). Link not available.
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KILLING OF AVIAN AND SWINE INFLUENZA VIRUS BY NATURAL KILLER CELLS
Virus Weekly
April 27, 2010

"In contrast, infection with the H5N1 virus resulted in high mortality rates, and ca. 60% of the infected patients succumb to the infection. Thus, one of the world greatest concerns is that the H5N1 virus will evolve to allow an efficient human infection and human-to-human transmission. Natural killer (NK) cells are one of the innate immune components playing an important role in fighting against influenza viruses. One of the major NK activating receptors involved in NK cell cytotoxicity is NKp46. We previously demonstrated that NKp46 recognizes the hemagglutinin proteins of B and A influenza virus strains. Whether NKp46 could also interact with H1N1-2009 virus or with the avian influenza virus is still unknown. We analyzed the immunological properties of both the avian and the H1N1-2009 influenza viruses. We show that NKp46 recognizes the hemagglutinins of H1N1-2009 and H5 and that this recognition leads to virus killing both in vitro and in vivo.”

"However, importantly, while the swine H1-NKp46 interactions lead to the direct killing of the infected cells, the H5-NKp46 interactions were unable to elicit direct killing, probably because the NKp46 binding sites for these two viruses are different."

The full article can be found at: (H. Achdout, et. al., “Killing of avian and Swine influenza virus by natural killer cells”. Journal of Virology, 2010;84(8):3993-4001). Link not available.
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IDENTIFICATION OF BROAD BINDING CLASS I HLA SUPERTYPE EPITOPES TO PROVIDE UNIVERSAL COVERAGE OF INFLUENZA A VIRUS
Virus Weekly
May 4, 2010

Our hypothesis is that influenza-derived HLA-class I-restricted epitopes can be identified for use as a reagent to monitor and quantitate human CD8(+) T-cell responses and for vaccine development to induce protective cellular immunity."

"Protein sequences from influenza A virus strains currently in circulation, agents of past pandemics and zoonotic infections of man were evaluated for sequences predicted to bind to alleles representative of the most frequent HLA-A and -B (class I) types worldwide. Peptides that bound several different HLA molecules and were conserved among diverse influenza subtypes were tested for their capacity to recall influenza-specific immune responses using human donor PBMC. Accordingly, 28 different epitopes antigenic for human donor PBMC were identified and 25 were 100% conserved in the newly emerged swine-origin H1N1 strain. The epitope set defined herein should provide a reagent applicable to quantitate CD8(+) T cell human responses irrespective of influenza subtype and HLA composition of the responding population.”

"In addition, these epitopes may be suitable for vaccine applications directed at the induction of cellular immunity."

The full article can be found at: (J. Alexander, et. al., “Identification of broad binding class I HLA supertype epitopes to provide universal coverage of influenza A virus”. Human Immunology, 2010;71(5):468-74). Link not available.
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FLU VIRUS TRANSPORTED BY DUST STORMS
Emerging Health Threats Forum
May 07, 2010

"Influenza viruses, including the avian H5N1 subtype, may be carried in the air for long distances and across continents by dust storms, according to new research in Taiwan. The concentration of influenza viruses in the air was found to be 20 to 30 times higher during dust storms than at other times.

The study is the first to measure influenza virus concentrations in ambient air, according to the authors. It follows a number of studies showing that airborne viruses can be found in indoor environments such as hospitals and offices."

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"The finding might explain why not all outbreaks of bird flu in animals have been linked to movement of poultry or wild birds, the authors say. "H5N1 outbreaks in South Korea and Japan were not consistent with either reported poultry trade or the timing and direction of migratory bird travel during the month of outbreak, suggesting that other factors led to these introduction events," they write. "Avian influenza outbreaks in downwind areas of Asian dust storms suggest that viruses might be transported by dust storms."

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"However, the impact of this finding on human health is unclear, argue Don Beezhold and John Noti of the US Centers for Disease Control and Prevention, in an email sent to EHTF news. "The amount of detected virus during Asian dust storm days was only 21 or 31 times higher," they say. "At best, this is only a modest increase in viral count."

Beezhold and Noti agree that viruses could get carried by air over very long distances.
"But the real question is whether the virus remains active," they write. "There are studies, including our own unpublished data, that indicate small amounts of aerosolized virus is infectious. The question is for how long and how far in the outdoor environment can viable virus travel?"

Influenza viruses can be inactivated by drying, ultraviolet radiation and atmospheric pollutants, explain Beezhold and Noti. All of these conditions would affect viruses in a dust storm. But the researchers also point to studies showing that by attaching to particles of dust, as might be expected during a dust storm, viruses can increase their chances of survival."

The full article can be found at: http://www.eht-forum.org/news.html?fileId=news100507061555&from=home&id=0

The original article can be found at: http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.0901782
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