2 February 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 #97

1. INFLUENZA B VIRUS CAUSES MILDER PATHOGENESIS AND WEAKER INFLAMMATORY RESPONSES IN FERRETS THAN INFLUENZA A VIRUS: *"Taken together, our results suggest that the lower induction of inflammatory cytokines and lower viral titers in the lungs may be responsible for the milder clinical signs seen in ferrets or humans infected with influenza B virus."*

2. INFLUENZA H5N1 VIRUS INFECTION OF POLARIZED HUMAN ALVEOLAR EPITHELIAL CELLS AND LUNG MICROVASCULAR ENDOTHELIAL CELLS: *"We demonstrate that both influenza H1N1 and H5N1 viruses efficiently infect alveolar epithelial cells from both apical and basolateral surface of the epithelium but release of newly formed virus is mainly from the apical side of the epithelium. In contrast, influenza H5N1 virus, but not H1N1 virus, efficiently infected polarized microvascular endothelial cells from both apical and basolateral aspects."*

3. HEMAGGLUTININ-DEPENDENT TROPISM OF H5N1 AVIAN INFLUENZA VIRUS FOR HUMAN ENDOTHELIAL CELLS: *"Overall, avian H5N1 viruses have a particular receptor specificity targeting endothelial cells that is different from human influenza viruses, and this H5N1 receptor specificity could contribute to disease pathogenesis."*

4. DNA SENSOR DEVELOPMENT BASED ON MULTI-WALL CARBON NANOTUBES FOR LABEL-FREE INFLUENZA VIRUS (TYPE A) DETECTION: *"The results show that the DNA sensor can detect as low as 0.5 nM of the target DNA samples; the response time of DNA sensor is approximately 4 min."*

5. IMMUNOSUPPRESSIVE HLA-G MOLECULE IS UPREGULATED IN ALVEOLAR EPITHELIAL CELLS AFTER INFLUENZA A VIRUS INFECTION: *"Thus the virulence of IAV may be caused by the capability of different strains to upregulate HLA-G allowing their escape from host immune responses."*

6. BINDING HOT SPOTS AND AMANTADINE ORIENTATION IN THE INFLUENZA A VIRUS M2 PROTON CHANNEL: *"In contrast, the NMR structure is based on a peptide/micelle construct that is able to accommodate the small molecular probes used for the mapping, but has a too narrow pore for the rimantadine to access the internal hot spot, and hence the drug can bind only at the exterior sites."*

7. HOST DEPENDENT EVOLUTIONARY PATTERNS AND THE ORIGIN OF 2009 H1N1 PANDEMIC INFLUENZA: *"Comparing the evolution of H1N1pdm ancestors with other influenza viruses, we show the evolutionary history in unsampled years is similar to the evolution of other swine viruses, presenting evidence it emerged from unsampled herds."*

8. EFFECTIVENESS OF COMMON HOUSEHOLD CLEANING AGENTS IN REDUCING THE VIABILITY OF HUMAN INFLUENZA A/H1N1: *"Importantly, however, our findings indicate that it is possible to use common, low-technology agents such as 1% bleach, 10% malt vinegar, or 0.01% washing-up liquid to rapidly and completely inactivate influenza virus."*

9. PROTECTION OF MICE AGAINST LETHAL CHALLENGE WITH 2009 H1N1 INFLUENZA A VIRUS BY 1918-LIKE AND CLASSICAL SWINE H1N1 BASED VACCINES: *"Our findings in mice agree with serological data showing high prevalence of 2009 H1N1 cross-reactive antibodies only in the older population, indicating that prior infection with 1918-like viruses or vaccination against the 1976 swine H1N1 virus in the USA are likely to provide protection against the 2009 pandemic H1N1 virus. This data provides a mechanistic basis for the protection seen in the older population, and emphasizes a rationale for including vaccination of the younger, naïve population. Our results also support the notion that pigs can act as an animal reservoir where influenza virus HAs become antigenically frozen for long periods of time, facilitating the generation of human pandemic viruses."*

CB Daily Report

Chem-Bio News

INFLUENZA B VIRUS CAUSES MILDER PATHOGENESIS AND WEAKER INFLAMMATORY RESPONSES IN FERRETS THAN INFLUENZA A VIRUS
Immunotherapy Weekly
January 27, 2010

“It is unknown why the influenza B virus causes less severe clinical signs than the influenza A virus in humans. Here we show that influenza B virus induces a lower levels of inflammatory cytokines in the lungs of infected ferrets, and causes less pathological damage to their lung tissues than does influenza A virus.”

"The copy numbers of inflammatory cytokine genes, such as TNF-alpha and IFN-alpha, was significantly lower in the lungs of ferrets infected with influenza B virus than in those infected with influenza A virus. There were also significantly lower viral titers in the lungs of ferrets infected with the influenza B virus than with the influenza A virus. In addition, the duration of viral presence was shorter in the lungs of ferrets infected with influenza B virus than with influenza A virus.”

"Taken together, our results suggest that the lower induction of inflammatory cytokines and lower viral titers in the lungs may be responsible for the milder clinical signs seen in ferrets or humans infected with influenza B virus."

The full article can be found at: (Y.H. Kim, et. al., “Influenza B Virus Causes Milder Pathogenesis and Weaker Inflammatory Responses in Ferrets Than Influenza A Virus”. Viral Immunology, 2009;22(6):423-430). Link not available.
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INFLUENZA H5N1 VIRUS INFECTION OF POLARIZED HUMAN ALVEOLAR EPITHELIAL CELLS AND LUNG MICROVASCULAR ENDOTHELIAL CELLS
Medical Letter on the CDC & FDA
January 24, 2010

“"The primary target cell for HPAI H5N1 virus in human lung is the alveolar epithelial cell. Alveolar epithelium and its adjacent lung microvascular endothelium form host barriers to the initiation of infection and dissemination of influenza H5N1 infection in humans. These are polarized cells and the polarity of influenza virus entry and egress as well as the secretion of cytokines and chemokines from the virus infected cells are likely to be central to the pathogenesis of human H5N1 disease. To study influenza A (H5N1) virus replication and host innate immune responses in polarized primary human alveolar epithelial cells and lung microvascular endothelial cells and its relevance to the pathogenesis of human H5N1 disease. We use an in vitro model of polarized primary human alveolar epithelial cells and lung microvascular endothelial cells grown in transwell culture inserts to compare infection with influenza A subtype H1N1 and H5N1 viruses via the apical or basolateral surfaces. We demonstrate that both influenza H1N1 and H5N1 viruses efficiently infect alveolar epithelial cells from both apical and basolateral surface of the epithelium but release of newly formed virus is mainly from the apical side of the epithelium. In contrast, influenza H5N1 virus, but not H1N1 virus, efficiently infected polarized microvascular endothelial cells from both apical and basolateral aspects. This provides a mechanistic explanation for how H5N1 virus may infect the lung from systemic circulation. Epidemiological evidence has implicated ingestion of virus-contaminated foods as the source of infection in some instances and our data suggests that viremia, secondary to, for example, gastro-intestinal infection, can potentially lead to infection of the lung. HPAI H5N1 virus was a more potent inducer of cytokines (e.g. IP-10, RANTES, IL-6) in comparison to H1N1 virus in alveolar epithelial cells, and these virus-induced

chemokines were secreted onto both the apical and basolateral aspects of the polarized alveolar epithelium."

"The predilection of viruses for different routes of entry and egress from the infected cell is important in understanding the pathogenesis of influenza H5N1 infection and may help unravel the pathogenesis of human H5N1 disease."

The full article can be found at: (M.C.W. Chan, et. al., "Influenza H5N1 virus infection of polarized human alveolar epithelial cells and lung microvascular endothelial cells". Respiratory Research, 2009;10():102). Link not available.
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HEMAGGLUTININ-DEPENDENT TROPISM OF H5N1 AVIAN INFLUENZA VIRUS FOR HUMAN ENDOTHELIAL CELLS
Genomics & Genetics Weekly
January 22, 2010

"While the biological basis of inefficient transmission is well documented, the mechanisms by which the H5N1 viruses cause fatal disease remain unclear. In the present study, we demonstrate that human pulmonary microvascular endothelial cells (hPMEC) had a clearly higher susceptibility to infection by H5N1 HPAIV than to infection by human influenza viruses. This was measurable by de novo intracellular nucleoprotein production and virus replication. It was also related to a relatively higher binding capacity to cellular receptors. After infection of hPMEC, cell activation markers E-selectin and P-selectin were upregulated, and the proinflammatory cytokines interleukin-6 and beta interferon were secreted. H5N1 virus infection was also associated with an elevated rate of cell death. Reverse genetics analyses demonstrated a major role for the viral hemagglutinin in this cell tropism."

"Overall, avian H5N1 viruses have a particular receptor specificity targeting endothelial cells that is different from human influenza viruses, and this H5N1 receptor specificity could contribute to disease pathogenesis."

The full article can be found at: (M. Ocanamacchi, et. al., "Hemagglutinin-Dependent Tropism of H5N1 Avian Influenza Virus for Human Endothelial Cells". Journal of Virology, 2009;83(24):12947-12955). Link not available.
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DNA SENSOR DEVELOPMENT BASED ON MULTI-WALL CARBON NANOTUBES FOR LABEL-FREE INFLUENZA VIRUS (TYPE A) DETECTION
Biotech Week
January 20, 2010

"This paper describes the DNA immobilization using carbon multi-walled nanotubes (MWCNTs) for direct and label-free detection of influenza virus (type A). The DNA probe was attached on the sensor surface by means of covalent bonding between the amine and phosphate groups of the DNA sequence."

"The interaction between the DNA probe and the MWCNTs were characterized by Fourier Transform Infrared (FTIR) spectrometry, Raman spectra. The hybridization of the DNA probe and the target DNA were detected by changes in the conductance on the surface of sensors leading to the change in the output signal of the system."

"The results show that the DNA sensor can detect as low as 0.5 nM of the target DNA samples; the response time of DNA sensor is approximately 4 min."

The full article can be found at: (Phuong Dinh Tam, et. al., "DNA sensor development based on multi-wall carbon nanotubes for label-free influenza virus (Type A) detection". Journal of Immunological

Methods, 2009;350(1-2):118-124). Link not available.
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IMMUNOSUPPRESSIVE HLA-G MOLECULE IS UPREGULATED IN ALVEOLAR EPITHELIAL CELLS AFTER INFLUENZA A VIRUS INFECTION
Immunotherapy Weekly
January 20, 2010

"However, increasing the production of immunosubversive molecules is a mechanism by which viruses escape host surveillance. In this regard, the nonclassical HLA class I molecule HLA-G displays strong tolerogenic properties. We show here that several strains of IAV differently upregulate HLA-G expression, at both the mRNA and protein levels, in alveolar epithelial cells."

"Thus the virulence of IAV may be caused by the capability of different strains to upregulate HLA-G allowing their escape from host immune responses."

The full article can be found at: (F. Lebouder, et. al., "Immunosuppressive HLA-G molecule is upregulated in alveolar epithelial cells after influenza A virus infection". Human Immunology, 2009;70(12 Sp. Iss):1016-1019). Link not available.
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BINDING HOT SPOTS AND AMANTADINE ORIENTATION IN THE INFLUENZA A VIRUS M2 PROTON CHANNEL
Drug Week
January 22, 2010

"Structures of truncated versions of the influenza A virus M2 proton channel have been determined recently by x-ray crystallography in the open conformation of the channel, and by NMR in the closed state. The structures cliff er in the position of the bound inhibitors."

"The x-ray structure shows a single amantadine molecule in the middle of the channel, whereas in the NMR structure four drug molecules bind at the channel's outer surface. To study this controversy we applied computational solvent mapping, a technique developed for the identification of the most druggable binding hot spots of proteins. The method moves molecular probes-small organic molecules containing various functional groups-around the protein surface, finds favorable positions using empirical free energy functions, clusters the conformations, and ranks the clusters on the basis of the average free energy. The results of the mapping show that in both structures the primary hot spot is an internal cavity overlapping the amantadine binding site seen in the x-ray structure. However, both structures also have weaker hot spots at the exterior locations that bind rimantadine in the NMR structure, although these sites are partially due to the favorable interactions with the interfacial region of the lipid bilayer. As confirmed by docking calculations, the open channel binds amantadine at the more favorable internal site, in good agreement with the x-ray structure."

"In contrast, the NMR structure is based on a peptide/micelle construct that is able to accommodate the small molecular probes used for the mapping, but has a too narrow pore for the rimantadine to access the internal hot spot, and hence the drug can bind only at the exterior sites."

The full article can be found at: (G.Y. Chuang, et. al., "Binding Hot Spots and Amantadine Orientation in the Influenza A Virus M2 Proton Channel". Biophysical Journal, 2009;97(10):2846-2853). Link not available.
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HOST DEPENDENT EVOLUTIONARY PATTERNS AND THE ORIGIN OF 2009 H1N1 PANDEMIC

INFLUENZA
By Alexander Solovyov, Benjamin Greenbaum, Gustavo Palacios, W. Ian Lipkin et al.
PloS Influenza
January 31, 2010

"The origin of H1N1pdm constitutes an unresolved mystery, as its most recently observed ancestors were isolated in pigs nearly a decade before it emerged in humans. One theory suggests imperfect surveillance of swine viruses caused the virus to be missed in swine herds. Other hypotheses point to the possibility of laboratory error or an avian intermediary. We show substitution bias classification identifies the host where a virus has been evolving. Comparing the evolution of H1N1pdm ancestors with other influenza viruses, we show the evolutionary history in unsampled years is similar to the evolution of other swine viruses, presenting evidence it emerged from unsampled herds."

The full article can be found at: http://knol.google.com/k/host-dependent-evolutionary-patterns-and-the-origin-of-2009-h1n1-pandemic?collectionId=28qm4w0q65e4w.1&position=1
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EFFECTIVENESS OF COMMON HOUSEHOLD CLEANING AGENTS IN REDUCING THE VIABILITY OF HUMAN INFLUENZA A/H1N1
By Jane S. Greatorex, Rosanna F. Page2, Martin D. Curran, Paul Digard, Joanne E. Enstone, Tim Wreghitt, Penny P. Powell, Darren W. Sexton, Roberto Vivancos, Jonathan S. Nguyen-Van-Tam
PloS One
February 01, 2010

"Abstract

Background

In the event of an influenza pandemic, the majority of people infected will be nursed at home. It is therefore important to determine simple methods for limiting the spread of the virus within the home. The purpose of this work was to test a representative range of common household cleaning agents for their effectiveness at killing or reducing the viability of influenza A virus.

Methodology/Principal Findings

Plaque assays provided a robust and reproducible method for determining virus viability after disinfection, while a National Standard influenza virus RT-PCR assay (VSOP 25, www.hpa-standardmethods.org.uk) was adapted to detect viral genome, and a British Standard (BS:EN 14476:2005) was modified to determine virus killing.

Conclusions/Significance

Active ingredients in a number of the cleaning agents, wipes, and tissues tested were able to rapidly render influenza virus nonviable, as determined by plaque assay. Commercially available wipes with a claimed antiviral or antibacterial effect killed or reduced virus infectivity, while nonmicrobiocidal wipes and those containing only low concentrations (<5%) of surfactants showed lower anti-influenza activity. Importantly, however, our findings indicate that it is possible to use common, low-technology agents such as 1% bleach, 10% malt vinegar, or 0.01% washing-up liquid to rapidly and completely inactivate influenza virus. Thus, in the context of the ongoing pandemic, and especially in low-resource settings, the public does not need to source specialized cleaning products, but can rapidly disinfect potentially contaminated surfaces with agents readily available in most homes."

The full article can be found at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0008987
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PROTECTION OF MICE AGAINST LETHAL CHALLENGE WITH 2009 H1N1 INFLUENZA A VIRUS BY 1918-LIKE AND CLASSICAL SWINE H1N1 BASED VACCINES

By Balaji Manicassamy, Rafael A. Medina, Rong Hai, Tshidi Tsibane, Silke Stertz, Estanislao Nistal-Villán, Peter Palese, Christopher F. Basler, Adolfo García-Sastre
PloS Pathogens
January 29, 2010

"Abstract

The recent 2009 pandemic H1N1 virus infection in humans has resulted in nearly 5,000 deaths worldwide. Early epidemiological findings indicated a low level of infection in the older population (>65 years) with the pandemic virus, and a greater susceptibility in people younger than 35 years of age, a phenomenon correlated with the presence of cross-reactive immunity in the older population. It is unclear what virus(es) might be responsible for this apparent cross-protection against the 2009 pandemic H1N1 virus. We describe a mouse lethal challenge model for the 2009 pandemic H1N1 strain, used together with a panel of inactivated H1N1 virus vaccines and hemagglutinin (HA) monoclonal antibodies to dissect the possible humoral antigenic determinants of pre-existing immunity against this virus in the human population. By hemagglutinination inhibition (HI) assays and vaccination/challenge studies, we demonstrate that the 2009 pandemic H1N1 virus is antigenically similar to human H1N1 viruses that circulated from 1918–1943 and to classical swine H1N1 viruses. Antibodies elicited against 1918-like or classical swine H1N1 vaccines completely protect C57B/6 mice from lethal challenge with the influenza A/Netherlands/602/2009 virus isolate. In contrast, contemporary H1N1 vaccines afforded only partial protection. Passive immunization with cross-reactive monoclonal antibodies (mAbs) raised against either 1918 or A/California/04/2009 HA proteins offered full protection from death. Analysis of mAb antibody escape mutants, generated by selection of 2009 H1N1 virus with these mAbs, indicate that antigenic site Sa is one of the conserved cross-protective epitopes. Our findings in mice agree with serological data showing high prevalence of 2009 H1N1 cross-reactive antibodies only in the older population, indicating that prior infection with 1918-like viruses or vaccination against the 1976 swine H1N1 virus in the USA are likely to provide protection against the 2009 pandemic H1N1 virus. This data provides a mechanistic basis for the protection seen in the older population, and emphasizes a rationale for including vaccination of the younger, naïve population. Our results also support the notion that pigs can act as an animal reservoir where influenza virus HAs become antigenically frozen for long periods of time, facilitating the generation of human pandemic viruses."

The full article can be found at: http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000745;jsessionid=027845377C6BE71F2BC9A402C87A843E
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