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Review

Animal models for influenza virus pathogenesis, transmission, and immunology

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ABSTRACT

In humans, infection with an influenza A or B virus manifests typically as an acute and self-limited upper respiratory tract illness characterized by fever, cough, sore throat, and malaise. However, influenza can present along a broad spectrum of disease, ranging from sub-clinical or even asymptomatic infection to a severe primary viral pneumonia requiring advanced medical supportive care. Disease severity depends upon the virulence of the influenza virus strain and the immune competence and previous influenza exposures of the patient. Animal models are used in influenza research not only to elucidate the viral and host factors that affect influenza disease outcomes in and spread among susceptible hosts, but also to evaluate interventions designed to prevent or reduce influenza morbidity and mortality in man. This review will focus on the three animal models currently used most frequently in influenza virus research – mice, ferrets, and guinea pigs – and discuss the advantages and disadvantages of each.

Contents

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1. Influenza in the human host

1.1. Pathogenesis of influenza viruses in humans

Within one to two days of infection with an influenza A or B virus, influenza disease most commonly manifests with the sudden onset of characteristic respiratory and systemic symptoms (Treanor, 2010). Respiratory symptoms, such as dry cough, pharyngitis, and nasal congestion and discharge, are often similar to those observed in other viral upper respiratory tract infections (URTIs). The systemic symptoms of influenza, including fever and chills, headache, myalgia, lethargy, and anorexia, develop early in the course of disease. Fever generally ranges from 100 °F to 104 °F (38 °C to 40 °C), but may be as high as 106 °F (41 °C), with peak temperatures on the first day of symptoms and decreasing over three to eight days thereafter (Treanor, 2010). The prominent presence of systemic symptoms is often said to differentiate influenza from other viral URTIs. However, considerable syndromic overlap exists among these viral illnesses, particularly in the elderly; thus, the phrase "influenza-like illness" (ILI) is often employed to describe clinically indistinguishable viral URTIs (Widmer et al., 2012; Woolpert et al., 2012; Haas et al., 2013). In typical uncomplicated influenza, systemic symptoms generally resolve earlier than respiratory symptoms like cough and sore throat, which may persist for several days to a week after systemic symptoms abate (Treanor, 2010).

Pulmonary complications of influenza virus infection include primary viral pneumonia and secondary bacterial pneumonia. Clinically, primary influenza viral pneumonia initially manifests like a typical uncomplicated URTI, but the acute infection rapidly progresses to the lower respiratory tract, accompanied by signs and symptoms of pneumonic involvement like cough, dyspnea, and hypoxemia. In contrast, secondary bacterial pneumonia occurs subsequent to a typical influenza URTI. After an initial clinical improvement lasting four to 14 days, recrudescence of fever, dyspnea, and cough with sputum signals the onset of bacterial pneumonia, particularly caused by staphylococcal or streptococcal species (Treanor, 2010).

In immunocompetent persons, epidemic (often called "seasonal") influenza is most often uncomplicated, remaining confined to the upper respiratory tract. Though primary viral pneumonia occurs rarely overall, women in late pregnancy or the early post-partum period, the elderly, and those with comorbid cardiovascular or lung disease are at a higher risk of developing this complication (Treanor, 2010; Mertz et al., 2013). Influenza pandemics, while relatively infrequent, usually result in higher morbidity and mortality than seasonal epidemics. Pandemic influenza viruses arise from reassortment, the creation of a genetically and antigenically new virus by "mixing-and-matching" viral genes from human and/or animal influenza viruses. These "antigenic shift" events introduce an immunologically novel influenza virus into the human population, which has no pre-existing immunity to it. During recent pandemics, including those of 1918, 1957, 1968, and 2009, younger people have been disproportionately affected by lower respiratory tract disease requiring hospitalization, relative to inter-pandemic years (Murata et al., 2007; Lapinsky, 2010; Treanor, 2010). Theories to explain the unusual morbidity and mortality of pandemic influenza among the young include an immunopathology specific to this age group (such as an antibody-dependent enhancement of disease in persons with particular, previous exposures to other seasonal influenza virus strains) and, conversely, immunoprotection in older adults (for example their exposure, many decades before, to influenza viruses that induced cross-protective immune responses that are not present in those who had yet to be born at that time) (Taubenberger and Morens, 2006).

The kinetic course of influenza virus replication in and then eradication from the human respiratory tract is often inferred from influenza challenge studies, in which human volunteers were experimentally inoculated with influenza viruses and then observed for symptomatic and virological measures of disease. A meta-analysis of human challenge studies (Carrat et al., 2008) found that, on average, viral shedding in nasal secretions begins within the first 24 h after inoculation, peaks on day 2, and ends by day 8 or 9 post-infection. Overall, only 66% of experimentally inoculated subjects developed disease; however, viral shedding could be detected even in asymptomatic persons. Average symptom scores peaked at three days post-infection (dpi), indicating that viral shedding precedes the development of disease by approximately one day (Carrat et al., 2008). The findings of this meta-analysis were echoed in a recent human challenge study (Y. Huang et al., 2011), in which 17 healthy volunteers were experimentally inoculated with influenza A/Wisconsin/67/2005 [H3N2], but only 9 (53%) developed symptomatic influenza. Infectious virus could be isolated from half of the asymptomatic volunteers, although viral shedding from symptomatic subjects was of greater magnitude and longer duration. Similar to the meta-analysis findings, in this study symptoms appeared, on average, between 1 and 2 days post-inoculation (range, 22 to 60 h). Changes in messenger RNA (mRNA) levels in peripheral blood mononuclear cells (PBMCs) were quantified by microarray every 8 to 24 h throughout the course of the study, in order to describe for each subject a specific gene expression signature in response to influenza virus infection. Interestingly, symptomatic and asymptomatic subjects displayed characteristic yet