Features of Animal Models of Influenza Infection

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Features of the Mouse Model

- Human influenza viruses replicate in the respiratory tract without prior adaptation but require adaptation to cause disease.
- Some avian influenza viruses, including HPAI H5N1 viruses replicate efficiently and cause disease without prior adaptation, though the extent of disease can vary even among closely related viruses.
- Receptor distribution in the respiratory tract: α 2,3 in ciliated airway and type II alveolar epithelial cells (H5N1 viruses bind to trachea).
- Clinical signs include ruffled fur, hunching, labored breathing, hypothermia, weight loss and mortality.
- Intranasal infection under anesthesia results in viral pneumonia.
- Some influenza isolates replicate in extrapulmonary sites. The significance is unknown but in H5N1 infections, extrapulmonary spread correlates with lethality.
- Doses of inactivated virus vaccines used in mice range from <1 to 10μg; usually administered with adjuvants such as complete or incomplete Freund's, Ribi or Al salts.
- Doses of live virus vaccines used in mice range from 10^5 -10^6 $TCID_{50}$

Features of the Ferret Model

- Human and avian influenza viruses replicate efficiently in the respiratory tract of ferrets without prior adaptation.
- Receptor distribution appears to be similar to humans: α 2,6 in the upper respiratory tract and α 2,3 in the alveoli.
- Clinical signs of illness include fever, sneezing, rhinorrhea and weight loss. Neurologic and gastrointestinal symptoms are seen following infection with some HPAI viruses.
- Mild inflammation is observed in the respiratory tract following infection with human influenza viruses.
- Some influenza viruses replicate in extrapulmonary sites e.g. brain. The significance of this finding is unknown.
- Doses of inactivated virus vaccines range from 7 to 15 μg. Generally administered with adjuvant or in two doses.
- Live virus vaccine dose is usually 10^7 $TCID_{50}$. Volume of inoculum should be 0.2 ml.

Hamster, Guinea Pig and Cotton Rat Models

Hamsters

- Human and avian influenza viruses replicate efficiently in the respiratory tract of hamsters without prior adaptation.
- Clinical signs of infection are not observed with human influenza viruses but some avian influenza viruses cause lethal infection.
- Extrapulmonary spread of some avian influenza viruses has been reported.

Guinea Pigs

- Human influenza viruses replicate efficiently in the respiratory tract of guinea pigs without prior adaptation. Avian influenza viruses have not been evaluated in this model.
- Hartley strain gp are highly susceptible to non-adapted A/Panama/99 (H3N2). Infection transmitted to contact animals.
- Clinical signs of infection are not observed with human influenza viruses.
- Pneumonia was observed with A/HK/1/68 (H3N2) infection.

Cotton Rats

- Non-adapted human influenza isolates replicate in the upper and lower respiratory tract following intranasal inoculation under light anesthesia.
- An increase in respiratory rate is a clinical sign of infection.
- Histopathological changes are observed in the lungs following infection.

Features of Cat and Non-human Primate Models

Cats

- Intranasal infection with human influenza viruses does not result in clinical signs of influenza. Virus can be recovered from pharyngeal secretions and can be transmitted to contact animals.
- H7 avian influenza viruses replicate in URT but do not cause illness.
- HPAI H5N1 viruses cause severe, lethal infection after intratracheal inoculation or feeding on infected bird carcasses.
- Binding to LRT similar to that in human tissue.
- HPAI H5N1 viruses replicate in extrapulmonary sites, including GI tract, and are transmitted to contact animals.

NHPs

- Inoculation by a variety of routes (e.g. intranasal + intratracheal) is needed to establish infection in NHP with human and avian influenza viruses.
- Some NHP species exhibit clinical signs of infection following intratracheal inoculation.
- HPAI H5N1 viruses cause some disease in cynomolgus macaques.

Advantages and Disadvantages of Mouse Models for Influenza

Advantages

- Wide range of strains of mice available with different genetic backgrounds for immunological studies.
- Wide range of immunological reagents available for studying humoral and cellular immune responses.
- Readily available and standard strains are relatively inexpensive.

Disadvantages

- Many influenza virus viruses require adaptation to cause disease and lethality.
- Standard lab strains of mice do not have a functional Mx gene.
- Level of anesthesia can affect outcome of infection.

Advantages and Disadvantages of Ferret Models for Influenza

Advantages

- Ferrets are naturally susceptible to influenza viruses.
- Clinical signs of infection are similar to human infection: fever and upper respiratory tract symptoms.

Disadvantages

- Difficult to obtain animals that are seronegative for human influenza viruses.
- Limited number of suppliers and limited immunological reagents
- Specialized housing requirements.
- Higher core body temperature may limit utility for evaluation of temperature sensitive viruses.

Advantages and Disadvantages of Non-human Primate Models for Influenza

Advantages

- Closer evolutionary relationship to humans

Disadvantages

- Require high doses of inoculum and multiple routes of inoculation (including intratracheal) to establish infection.
- Expensive and require specialized housing.