Influenza Infections

Influenza viruses of type A infect humans, pigs, horses, and birds and are the major cause of pandemic and epidemic influenza infections. The influenza genome encodes a number of proteins, but the most important from the vantage point of viral virulence are the hemagglutin and neuramindase proteins. Hemagglutinin has three major subtypes (H1-H3), while neuraminidase has two (N1, N2). Both proteins are components of the influenza virus envelope, which consists of a lipid bilayer. Hemagglutinin is particularly important, as it serves to attach the virus to its cellular target via sialic acid residues on surface polysaccharides. Following uptake of the virus into endosomal vesicles, acidification of the endosome triggers a conformation change in hemagglutinin that allows the viral envelope to fuse with the host cell membrane, releasing the viral genomic RNAs into the cytoplasm of the cell. Neuraminidase in turn facilitates the release of newly formed virions that are budding from infected cells by cleaving sialic acid residues. Neutralizing host antibodies against viral hemagglutinin and neuraminidase prevent and ameliorate, respectively, infection with the influenza virus by interfering with these functions.

The viral genome is composed of eight single-stranded RNAs, each encoding one or more proteins. The RNAs are packaged into helices by nucleoproteins that determine the influenza virus type (A, B, or C). A single subtype of influenza virus A predominates throughout the world at a given time. Epidemics of influenza are caused by spontaneous mutations that alter antigenic epitopes on the viral hemagglutinin and neuraminidase proteins. These antigenic changes (*antigenic drift*) result in new viral strains that are sufficiently different to elude, at least in part, anti-influenza antibodies produced in members of the population in response to prior exposures to other flu strains. Usually, however, these new strains bear sufficient resemblance to prior strains that some members of the population are at least partially resistant to infection. By contrast, pandemics, which are longer and more widespread than epidemics, occur when both the hemagglutinin and the neuraminidase genes are replaced through recombination with animal influenza viruses (*antigenic shift*). In this instance, essentially all individuals are susceptible to the new influenza virus. Viral assembly involves packaging of each of the 8 viral RNAs into single virions, and it is easy to see how infection of an animal by two different flu types could lead to swapping of genetic material within co-infected cells, creating a completely new viral strain. Thus, the unusual genome of influenza virus ensures that antigenic shifts leading to pandemics are inevitable.

If the host lacks protective antibodies, the virus infects pneumocytes and elicits several cytopathic changes. Shortly after entry into pneumocytes, the viral infection inhibits sodium channels, producing electrolyte and water shifts that lead to fluid accumulation in the alveolar lumen. This is followed by the death of the infected cells through several mechanisms, including inhibition of host cell mRNA translation and activation of caspases leading to apoptosis. The death of epithelial cells exacerbates the fluid accumulation and releases "danger signals" that activate resident macrophages. In addition, prior to their death, infected epithelial cells release a variety of inflammatory mediators, including several chemokines and cytokines, adding fuel to the inflammatory fire. In addition, mediators released from epithelial cells and macrophages activate the nearby pulmonary endothelium, allowing neutrophils to attach and extravasate into the interstitium within the first day or two of infection. In some cases viral infection may cause sufficient lung injury to produce the acute respiratory distress syndrome, but more often severe and sometimes fatal pulmonary disease stems from a superimposed bacterial pneumonia. Of these, secondary pneumonias caused by *Staphylococcus aureus* are particularly common and often life-threatening.

Control of the infection relies on several host mechanisms. The presence of viral products induces innate immune responses in infected cells, such as the production of α- and β-interferon. These mediators upregulate the expression of the *MX1* gene, which encodes a GTPase that interferes with influenza gene transcription and viral replication. As with other viral infections, natural killer cells and cytotoxic T cells can recognize and kill infected host cells, limiting viral replication and viral spread to adjacent pneumocytes. The cellular immune response is eventually augmented by development of antibody responses to the viral hemagglutinin and neuraminidase proteins.

Insight into future pandemics has come from studying those past. DNA analysis of viral genomes retrieved from the lungs of a soldier who died in the great 1918 influenza pandemic that killed between 20 million and 40 million people worldwide identified swine influenza sequences, consistent with this virus having its origin in a "antigenic shift". The first flu pandemic of this century, in 2009, was also caused by an antigenic shift involving a virus of swine origin. It caused particularly severe infections in young adults, apparently because older adults had antibodies against past influenza strains that conveyed at least partial protection. Comorbidities such as diabetes, heart disease, lung disease, and immunosuppression were also associated with a higher risk of severe infection.

What then might be the source of the next great pandemic? There is no certainty, but one concern is centered on avian influenza, which normally infects birds. One such strain, type H5N1, has spread throughout the world in wild and domestic birds. As of June 2011, a total of 562 H5N1 influenza virus infections and 325 deaths in humans (from 15 countries) have been reported to the World Health Organization (WHO). Nearly all cases have been acquired by close contact with domestic birds; most deaths resulted from pneumonia. Fortunately, the transmission of the current H5N1 avian virus is inefficient. However, if H5N1 influenza recombines with an influenza that is highly infectious for humans, a strain might result that is capable of sustained human-to-human transmission (and, thus, of causing the next great pandemic).

Human Metapneumovirus

Human metapneumovirus (MPV), a paramyxovirus discovered in 2001, is found worldwide and is associated with upper and lower respiratory tract infections. It can infect any age group but is most commonly seen in young children, elderly subjects, and immunocompromised patients. Human MPV can cause severe infections such as bronchiolitis and pneumonia and is responsible for 5% to 10% of hospitalizations and 12% to 20% of outpatient visits of children suffering from acute respiratory tract infections. Such infections are clinically indistinguishable from those