VIRAL IMMUNITY

Bad memories

Seasonal strains of influenza virus cause more severe disease in infants and the elderly, but historically, pandemic strains of influenza virus have induced the most debilitating disease in healthy young adults. A study in *Nature Medicine* now offers an explanation for this paradox.

To explore the mechanisms by which pandemic strains of influenza virus promote disease, the authors characterized samples from patients who had been infected with either pandemic or seasonal strains of influenza virus. Pandemic strains of influenza virus have been proposed to cause disease by inducing a 'cytokine storm'; however, nasopharyngeal secretions from patients with pandemic or seasonal influenza contained similar levels of inflammatory cytokines. Furthermore, monocytes from healthy donors showed similar cytokine induction following culture with haemagglutinin 1 (HA1) from pandemic or seasonal influenza virus.

The authors next measured the levels of HA1-specific antibodies in healthy individuals of different ages. IgG antibodies specific for viral HA1 were not detected in infants, but could be found in sera from young and elderly adults. However, although the HA1-specific antibodies from elderly adults could neutralize and protect against a pandemic influenza virus strain from 2009, antibodies from young adults showed lower avidity and could not neutralize the virus. This was despite the fact that antibodies from the young adults showed higher avidity for a seasonal influenza virus. Young adults who became severely ill during the 2009 pandemic had higher serum levels of HA1-specific IgG than those who developed mild disease, but the HA1-specific antibodies from the severely ill individuals showed lower overall avidity for the 2009 influenza virus strain. Together, these data suggest that high levels of low-avidity antibody, which was probably generated during previous seasonal influenza virus infections, promoted severe disease during the 2009 influenza virus pandemic.

Low-avidity antibody responses are associated with immune complex-mediated disease, and in keeping with this, extensive deposition of the complement component C4d was seen in lung sections from young adults who were fatally infected during the 2009 pandemic. In addition, although immune complexes were detected in secretions from patients with pandemic influenza, they were rarely found in secretions from patients with seasonal influenza. Finally, extensive deposition of C4d was observed in archived lung sections from adults who died during a 1957 influenza pandemic, indicating that immune complex-mediated disease may also have contributed to fatal cases during this pandemic.

These findings offer a plausible explanation for the unusual age distribution of severe cases that occurs during influenza virus pandemics. Healthy young adults are more likely to have pre-existing antibodies to seasonal strains of influenza virus, and these antibodies cross-react with the pandemic strain but are non-protective. Instead, the low-avidity antibodies promote the deposition of immune complexes in the lung, leading to severe, and often fatal, respiratory disease.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Monsalvo, A. C. *et al.* Severe pandemic 2009 H1N1 influenza disease due to pathogenic immune complexes. *Nature Med.* 5 Dec 2010 (doi:10.1038/nm.2262)