INNATE IMMUNITY

1918 — a lesson from history?

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The influenza A virus that was responsible for the 1918 pandemic was particularly severe, infecting one-third of the world's population and resulting in millions of deaths. In a recent *Nature* paper, Kobasa *et al.* published the first study on the pathogenicity of the 1918 virus in non-human primates. Their results indicate that the ability of the 1918 virus to modulate host immune responses could have contributed to its unprecedented lethality.

Using a cynomolgus macaque model, Kobasa *et al.* carried out a comparative virological and functional genomic analysis of animals infected with the 1918 virus and control animals infected with a contemporary human H1N1 influenza virus, K173. They found that, in K173-virus-infected animals, the virus was restricted to a small area of the respiratory tract, causing mild clinical symptoms. Whole-genome analysis of gene-expression patterns showed a dynamic innate immune response, in which the amount of protein expressed correlated with the amount of virus present in the tissues. For example, an increase in type 1 interferon genes was observed in the early stages of infection (when viral load was highest), which was downregulated later in infection (when the virus had been cleared). The authors concluded that infection with K173 elicits a dynamic host response that facilitates viral clearance and recovery of the animal.

By contrast, the 1918 virus was present in higher titres throughout the respiratory tissues, and showed progressive damage. Analysis of gene-expression patterns showed that the 1918 virus caused an aberrantly high and sustained expression of genes involved in the innate immune response, including pro-inflammatory cytokines. Interleukin (IL)-6 (thought to have a role in mediating the clinical manifestation of infection), increased by up to 25-fold, whereas levels remained the same in K173-virus-infected animals throughout the experiment. Although essential for host defence, an extreme innate immune response can be harmful and can contribute to viral pathogenicity through an excessive infiltration of immune cells leading to tissue destruction, an outcome that was consistent with the symptoms observed. Therefore, the authors suggest that this atypical expression of the innate immune response was a crucial factor in determining the severity and outcome of infection by the 1918 virus.

The ability of the 1918 virus to modulate host immune responses might be a characteristic that is shared by other virulent influenza viruses. The recent emergence of the H5N1 avian influenza virus, and its implications for humans, highlights the need for a better understanding of the transmission of pandemic influenza viruses, their interactions with the host and their ability to modify host innate immune responses.

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ORIGINAL RESEARCH PAPER Kobasa, D. *et al.* Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature* **445**, 319–323 (2007)