NEWS & VIEWS

INFLUENZA

Fatal immunity and the 1918 virus

Yueh-Ming Loo and Michael Gale Jr

Innate immune defences are our first line of protection against infection by viruses and are essential in limiting viral disease. But their reaction to the 1918 influenza virus could have been deadly.

The devastating Spanish influenza A virus infected around a third of the world's population during the pandemic of 1918. With mortality rates more than 25 times that of other influenza pandemics, the 1918 virus killed over 40 million people worldwide[1]. Influenza A virus is transmitted among humans and domestic animals, and when different strains infect the same cell, mixing of the two viral genomes (or 'reassortment') can generate new strains with epidemic or pandemic potential.

Studies of genetically engineered influenza A viruses containing some or all of the genes from the 1918 virus suggest that this virus might have acquired a unique combination of genes that caused the disease's unusual severity[1,2]. However, the specific actions of these genes and their contribution to the virulence of the 1918 pandemic have remained elusive. On page 319 of this issue, Kobasa *et al.*[3] provide the first report of the effects of the reconstructed 1918 influenza virus in monkeys. Their findings link the unprecedented lethality of the 1918 pandemic virus to an aberrant innate immune response.

During infection, an invading virus is recognized by specialized cellular proteins that engage viral nucleic acids or proteins and trigger signalling pathways within the infected cell. These pathways culminate in the production of molecules of the innate immune system — our first line of protection against infection — called α/β-interferons, proinflammatory cytokines and chemokines[4]. This group of proteins includes interleukins, which are essential for activating immune cells, and chemoattractant proteins, which recruit immune cells to sites of infection. The innate immune response is triggered over a course of minutes to hours after infection, and these secreted proteins act collectively, both locally and systemically, to direct the expression of a wide range of proteins that act directly against the virus or stimulate inflammation. However, unchecked or excessive stimulation of the innate immune response can be harmful. It can contribute to the virulence of pathogenic viruses, in part by causing excessive infiltration of the tissues by immune cells, resulting in tissue destruction[5].

Kobasa *et al.*[3] conducted comparative virological and functional-genomic analyses of monkeys infected with either a contemporary influenza virus or the 1918 pandemic virus. Influenza virus strains are generally classified by the two proteins that vary most widely among them — haemagglutinin (H) and neuraminidase (N). Both of the viruses in Kobasa and colleagues' study are of the H1N1 type, although they differ in their epidemiological and pathological properties because of variations in their other proteins.

Analysis of the animals infected with the contemporary virus showed that the virus was present in only a small area of the respiratory tract, causing mild symptoms. Gene expression patterns in the cells lining the bronchus confirmed a robust innate immune response soon after infection. This response included the induction of α/β-interferons, cytokines and chemokines, but the expression of each of these proteins was transient and correlated directly with virus levels in the infected tissues. The authors therefore conclude that infection with contemporary H1N1 influenza virus elicits a transient but appropriate activation of innate immune defences that ultimately facilitates clearance of the virus and recovery.

By comparison, the 1918 virus replicated to high levels and spread rapidly throughout the respiratory tract of infected animals. Lung tissue from these animals showed severe

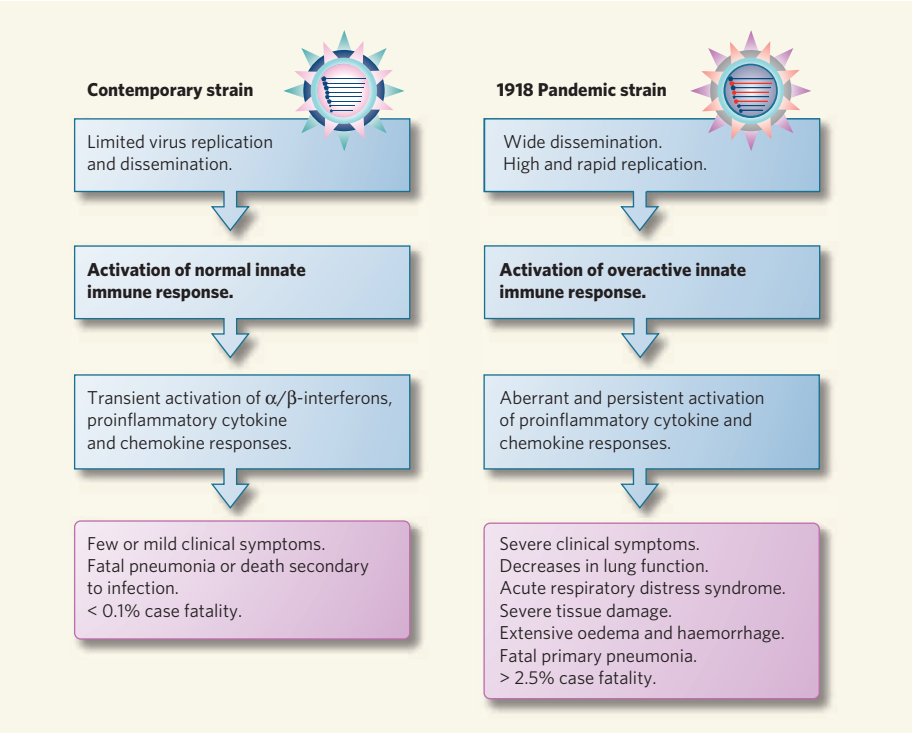

Figure 1 | Different responses to influenza A virus infections. The innate immune response provides protection against virus infection and limits viral disease. Contemporary influenza virus strains induce a transient innate immune response that typically follows a course of self-limiting infection, producing only mild symptoms in patients. Serious disease from contemporary influenza virus is often due to secondary causes. However, the reconstructed 1918 influenza A virus aggressively replicates and disseminates in monkey and mouse models of infection[3,10], and induces an aberrant innate immune response. This could be the cause of the increased severity of symptoms and more deaths in infected people. Blue, observations in animal models; purple, clinical observations in humans.

damage, including bleeding and infiltration of immune cells, at times well after the peak of virus replication. A whole-genome analysis of gene expression — the first in monkeys infected with the 1918 virus — showed that the virus triggered aberrantly high and sustained expression of genes encoding many proteins involved in the innate immune response, including proinflammatory cytokines and chemokines. So Kobasa *et al.*[3] propose that an aberrant innate immune response to the 1918 influenza virus could be responsible for the rapid, severe outcome of the infection (Fig. 1). Their data suggest that persistent elevation of inflammatory-response genes could account for the massive inflammation and infiltration of immune cells observed in the respiratory tract of animals infected with the 1918 virus.

Notably, infection with contemporary influenza virus triggered robust expression of genes encoding several α-interferon subtypes and of interferon-stimulated genes with known antiviral properties, and this expression was associated with the comparative mildness of the disease. By contrast, the 1918 virus induced only low and selective expression of genes encoding α-interferon subtypes and differential expression of many interferon-stimulated genes — including one that encodes a protein called RIG-I. Contemporary influenza A virus triggers innate immune defences in part through RIG-I, which regulates the expression of other immune and inflammation genes[6]. But tissue infected with the 1918 virus showed reduced RIG-I expression compared with tissue infected with the contemporary virus. Although these observations may conceptually link RIG-I activity to intracellular pathways that would normally induce the production of interleukins and chemoattractants to clear the virus, the study lacks the biochemical data that are essential for defining such connections.

Kobasa *et al.*[3] demonstrate the power of functional genomics in untangling the complexities of virus–host interactions and viral pathogenesis. Their gene-expression profile analyses suggest that the 1918 virus triggers innate immune signalling processes that possess altered kinetics relative to the contemporary influenza A virus, and/or that the 1918 virus may selectively attenuate the expression of specific innate-response genes. The authors did not, however, analyse gene expression during the important early time course of these events (the first hours and days of infection), so determining the exact mechanisms regulating gene expression will take further study. But it is worth mentioning one possible candidate molecule: the nonstructural-1 (NS1) protein of the influenza A virus can suppress innate immunity by disrupting the induction of α/β-interferon and/or altering the maturation of host-cell RNA[7,8]. Of course, NS1 does not work alone[9], and virulence attributed to pandemic influenza requires many viral components in a unique assemblage of genes[1,2].

The work of Kobasa *et al.* substantiates the findings of Kash *et al.*[10], who showed in mice that the 1918 virus triggered a vigorous innate immune response that was linked to fatalities. Although the mechanisms of tissue destruction were not addressed in either study, the work clearly demonstrates the vital function of early innate immune defences in controlling the virus. It seems that the pandemic 1918 virus had a genetic composition and rapid replication kinetics that may have resulted in an excessively vigorous innate immune and inflammatory response that contributed to severe tissue damage, disease and death.

These conclusions correspond to the striking epidemiological data showing that, unlike contemporary influenza strains, which typically affect the very young and the elderly most severely, the 1918 influenza pandemic was mostly fatal in young adults, who generally possess more robust immune systems[1]. Unveiling the contribution of an aberrant host response to the pathogenesis of the 1918 virus is just the beginning of efforts to understand the disease mechanisms underlying the 1918 pandemic and new virulent strains of influenza virus. The emergence of the H5N1 avian influenza or 'bird flu' virus, and its transfer to the human population, are real and continuing threats[1] that underscore the importance of the current study and of characterizing highly pathogenic forms of flu virus. A better understanding of the origin, transmission and virulence of pandemic influenza viruses, and their interactions with host immune processes, will assist our preparation against future and possibly deadly influenza pandemics. ■

Yueh-Ming Loo and Michael Gale Jr are in the Department of Microbiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9048, USA.
e-mail: michael.gale@utsouthwestern.edu

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SEMICONDUCTOR ELECTRONICS

Trapped fast at the gate

Gerwin Gelinck

The speed record for programming organic transistor memory has been shattered. Work is needed on the stability of the memory storage, but it's a promising step towards some novel technological applications.

The advent of non-volatile flash memory — semiconductor memory that does not lose its data when the power is turned off — revolutionized consumer electronics. It is now used to store the numbers in mobile phones, the pictures taken with digital cameras, and the music tracks in MP3 players. Similar types of memory based on organic semiconductors, rather than traditional silicon-based semiconductors, would make possible entirely new concepts: intelligent food packaging, for instance, that could be used by retailers to control their inventories and to alert consumers when the food is getting close to its 'use-by' date. Writing in *Advanced Materials*, Baeg *et al.*[1] describe an organic thin-film memory transistor that brings such intriguing possibilities a little closer.

Two particular advantages of organic thin-film transistors over solid-state transistors are that they are simpler to make, and can be fabricated on thin, flexible plastic substrates. They could thus form the backbone of low-cost microelectronics ranging from radio-frequency identification tags to flexible, large-area active-matrix displays[2]. Many of these applications require non-volatile (stable) data storage, preferably with memory elements that can be programmed, erased and read electrically. Baeg and colleagues' transistor[1] not only fulfils these requirements, but can also, owing to its similar architecture, be simply integrated into existing technology based on organic transistors.

In order to function as a memory, a device must be observed in two (or more) different states. In flash memories, this is achieved by introducing a second 'floating gate' to the silicon transistor between the normal control gate, which regulates the flow of current through the transistor, and the semiconducting substrate (Fig. 1a). This floating gate is insulated all around by an oxide layer. A high-voltage pulse applied to the control gate places charge on the floating gate, where it becomes trapped. This partially cancels out the electric field coming from the control gate, and so modifies the threshold voltage of the transistor — that is, the voltage required before it lets current flow. Thus, when the transistor is 'read' by placing a specific voltage on the control gate, electrical current will either flow or not flow, depending on the threshold voltage, and so the number of electrons on the floating gate. The resulting