GENOME WATCH

The chronicles of virus–host affairs

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This month's Genome Watch highlights a new large-scale serological platform for the simultaneous detection of multiple human viruses in a single drop of blood.

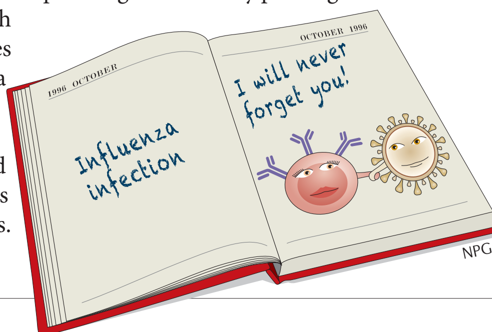
Exposure to pathogens can have immediate and long-term effects on our health, leaving a distinctive footprint in the form of immunological memory. Long-lived immune cells act as a record of host–pathogen interactions, storing a large pool of antigen-specific information, which confers protection and provides a quick response upon re-exposure. Exploring the immune memory enables the identification of past and present infections and is an alternative approach to direct pathogen detection. Current methods that identify pathogen exposure are based on multiplex RT-PCR of viral genomes or serological tests directed to well-known epitopes recognized by the immune memory; these methods can only detect a small number of pathogens at a time[1]. Although important for basic diagnostic testing, these techniques have limited capacity to reveal previous pathogen exposures or to capture novel rapidly mutating viruses, which may pose an epidemic threat.

Recently, Xu *et al.* developed VirScan[2], a high-throughput serological screen that combines molecular biology techniques, publicly available sequence databases, high-throughput sequencing and bioinformatics to simultaneously identify antibodies against more than 206 human viruses. The method is based on a library of overlapping short peptides representing known and predicted viral epitopes, which are expressed in bacteriophages. After incubation with human serum, the antibody-bound phages are isolated and sequenced on the Illumina HiSeq 2000/2500 platform to identify the recognized epitope. Mapping the sequencing reads to the reference library identified an average of 10 (and a maximum of 84) virus species per person across 569 individuals. Using VirScan, the study identified commonly recognized epitopes across individuals and also found that specific serological profiles were associated with age, geographical origin and HIV status. A key strength of VirScan is its potential for epitope discovery, which can aid vaccine development by uncovering sites that are under selective immune pressures. The ability to investigate the immune response to predicted epitopes of many viruses in one assay would be invaluable for detecting novel viruses with unknown epitopes.

One limitation of VirScan is the potential underestimation of exposure to viruses with multiple strains that lack cross-protection. For diverse viruses such as influenza virus, a single representative epitope in the VirScan library is insufficient to reveal true exposure, as it may not be recognized by antibodies raised against other strains. A possible solution is the multiplexed virus detection method used by Shafer *et al.*[3], in which an improved RNA FISH (fluorescent *in situ* hybridization) assay is applied to viral RNA. By updating the RNA probes with newly sequenced virus variants, RNA FISH can distinguish between viral strains at the single-nucleotide level. Similarly, tailoring the VirScan library to include proteomes of current circulating strains could improve both sensitivity and specificity. This highlights the need for rapid and continuous whole-genome virus sequencing to maintain public databases, particularly in the context of emerging infectious threats.

In theory, an advantage of serological profiling over directly probing for viral RNA is the identification of past — in addition to ongoing — infections. However, VirScan detected a prevalence of measles virus antibodies of only 1.7% for individuals residing in the United States[2], which was unexpectedly low given that measles has a national vaccination coverage of more than 90%[4]. It is likely that exposure to measles was underestimated because measles-neutralizing antibodies mostly recognize conformational epitopes, rather than the unmodified linear peptides used in VirScan. To identify pathogens for which the major antibody targets are conformational or have post-translational modifications, a peptide screen should be complemented with technologies expressing full-length proteins, such as protein microarrays[5].

Despite these limitations, VirScan greatly advances our capacity to study viral infections. This technology could be used clinically as a 'first-pass' diagnostic tool (for any pathogen) or as a research tool to improve our understanding of host–pathogen dynamics.



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Competing interests statement
The authors declare no competing interests.

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