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The art of war: battles between virus and host

Perspective

Matthew Frieman

Addresses
University of Maryland School of Medicine, Baltimore, MD 21201, USA

Corresponding author: Frieman, Matthew (mfrieman@som.umaryland.edu)

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As Sun Tzu wrote in The Art of War, 'All warfare is based on deception'. He could have easily been describing the ancient battle between virus and host rather than on the lore of Chinese warfare. A virus must infect, replicate and spread for it to survive; the host attempting to thwart it at every step of the way. This ancient battle has been waged for millions of years and has spawned an innumerable number of viruses, each with their own unique ways of trying to outsmart the host. Some viruses encode proteins that directly inhibit/degrade/alter host pathways and some simply have evolved ways to hide from the hosts detection system. The host is not passive in this battle. It has evolved complex pathways and redundant mechanisms to respond to viral interlopers.

In the last 70 years, scientists have used viruses to illuminate many of the secrets that the host uses to fight back against the hoard. It was a virus that taught us about an 'interfering' molecule that is secreted from cells during infection and can be used to then protect other cells around it from subsequence infection [1]. This molecule is known as Interferon and has lead to treatments for numerous viral and inflammatory diseases such as Hepatitis C, Multiple Sclerosis and Cancer [2–4]. The more we understand how viruses interact with the host the more we can modify them for good; as vectors to deliver antigens as vaccines, as gene therapy delivery vehicles and as targeted cancer destroying missiles [5].

In this set of reviews collected in *Current Opinion in Virology*, we highlight new ways in which the interaction between virus and host is studied.

We start with John Schoggins reviewing the roles that Interferon-stimulated genes (ISGs) play in protecting the host from viruses. That same Interferon that was discovered over 60 years ago by Isaacs and [1,6], has been found to induce hundreds of genes only some of which have a known mechanism of action and anti-viral activity [7]. Schoggins highlights several ISGs that have been mechanistically deciphered and points out the striking finding that all viruses are not inhibited by each ISG. Rather, there is a virus, cell and tissue specific induction and interaction between each ISG and each virus species. Recent *in vivo* work has begun to decipher the specific interaction between an ISG and a virus. For example, take the case of Interferon stimulated gene 15 (ISG15) which is a small ubiquitin-like molecule that can become conjugated to proteins in the same way that ubiquitin can, often excluding ubiquitin from the same site. ISG15−/− mice are highly susceptible to Influenza virus however have no increased sensitivity to the alphavirus, Chikungunya. A deeper understanding of how the ISG proteins interact with each viral species is needed to identify which are important therapeutic targets.

In the context of viral entry, Berend Jan Bosch and colleagues focus on the viral receptors for Coronaviruses. Two highly pathogenic Coronaviruses have emerged in the last decade, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the newly discovered Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [8]. This is in addition to known human coronaviruses, which cause common cold symptoms (e.g. hCoV-229E, hCoV-OC43) and economically important porcine coronaviruses (e.g. Porcine Epidemic Diarrhea Virus, PEDV). Interestingly, 4 of the 6 human Coronaviruses have evolved to utilize endopeptidases expressed on either the respiratory or intestinal tract, including MERS-CoV. Jan Bosch points out the nature of this interaction and how the moderately conserved nature of each endopeptidase between species could allow for viral spillover from one host species to the next. As SARS-CoV, the ACE2 receptor on host cells is expressed in palm civets and bats, and a recent finding of a SARS-like bat virus capable of using human ACE2 for entry demonstrates the ability of Coronaviruses to jump from one species to another. The ability of Coronaviruses to spread from one species to the other has occurred throughout recent history. The porcine coronavirus, Transmissible Gastroenteritis Virus (TGEV) evolved from the Canine Coronavirus with prominent Spike mutations allowing for the species shift from dog to cow [9]. Variants of the normally self-limiting canine coronavirus have also arisen that confer high mortality rates in dogs, with mutations

found in the Spike protein [10]. This leads us to hypothesize that the direct interaction between viral Spike protein and receptor is even more than just for binding of the virion to the cell. Further research on the effect of how Coronavirus:receptor interactions affect pathogenesis are needed to understand this intimate and critical association.

The continued expansion of a holistic or 'systems biology' approach to characterizing the effects of a pathogen on its host have identified many new avenues of explore in the virus:host arms race. In recent work, a reductionist approach has proved very productive to identify single host factors that modulate viral pathogenesis. What we have learned from these many studies is that there is a delicate balance between the host response to infection that protects us from disease and the imbalance that can occur that can cause more disease. The ability to simultaneously investigate diverse pathways using transcriptomics, proteomics and diverse mouse strains allows for a broader appreciation of the interconnectivity of the host response to disease. These new techniques also allow for precise understanding of how the response to infection can be modulated at other pathways outside of what we knew before and potentially at specific nodes of cross regulation such that a single therapeutic intervention could modulate multiple pathways to benefit the host.

In Suthar *et al.*, he reviews how systems biology approaches to West Nile virus (WNV) infection have identified novel host targets uniquely modulated during WNV infection. Schafer *et al.* review the current understanding of Coronavirus pathogenesis in light of new systems biology approaches that utilize large sets of intercrossed mouse strains, called the Collaborative Cross, to identify new genes implicated in Coronavirus disease induction. Heinke Kollmus *et al.* profiles the current systems biology approaches to Influenza virus infection and pathogenesis. For Influenza virus pathogenesis studies, Killmus *et al.* discuss how the Collaborative cross in connection with transcriptome and proteomic analysis can be combined to synergistically pinpoint genes and alleles that modulate disease severity. Through all of the systems biology approaches, the key link is the ability to model how the intertwined host response to infection combines into the induction of proteins that attempt to inhibit viral infection. The paradigm of multi-pathway analysis now exists to compare across viruses, hosts and routes of infection, how disease is initiated, how it differs between variables and how all of these factors can point the research into targeted therapies for broad ranges of viral infections.

Importantly, these reviews highlight the continued and basic need for research into how viruses cause disease. We know that we must be prepared for the next MERS-CoV or Chikungunya virus outbreak and with these new approaches to understanding pathogenesis we can identify how these viruses attack. The only question is, can we figure out their battle plans before it is too late.

References

1. Isaacs A, Lindenmann J: **Virus interference. I. The interferon**. *Proc R Soc Lond B Biol Sci* 1957, **147**:258-267.
2. St Geme JW Jr: **Therapeutic control of viral infections: chemotherapy, interferon and gamma globulin**. *Curr Problems Pediatr* 1979, **10**:1-46.
3. Panitch HS: **Early treatment trials with interferon beta in multiple sclerosis**. *Multiple Sclerosis* 1995, **1(Suppl 1)**:S17-S21.
4. Krown SE: **Interferons and interferon inducers in cancer treatment**. *Seminars Oncol* 1986, **13**:207-217.
5. Usme-Ciro JA, Campillo-Pedroza N, Almazan F, Gallego-Gomez JC: **Cytoplasmic RNA viruses as potential vehicles for the delivery of therapeutic small RNAs**. *Virol J* 2013, **10**:185.
6. Isaacs A, Lindenmann J, Valentine RC: **Virus interference. II. Some properties of interferon**. *Proc R Soc Lond B Biol Sci* 1957, **147**:268-273.
7. Schoggins JW, Rice CM: **Interferon-stimulated genes and their antiviral effector functions**. *Curr Opin Virol* 2011, **1**:519-525.
8. Coleman CM, Frieman MB: **Coronaviruses: important emerging human pathogens**. *J Virol* 2014.
9. Laude H, Rasschaert D, Delmas B, Godet M, Gelfi J, Charley B: **Molecular biology of transmissible gastroenteritis virus**. *Vet Microbiol* 1990, **23**:147-154.
10. Buonavoglia C, Decaro N, Martella V, Elia G, Campolo M, Desario C, Castagnaro M, Tempesta M: **Canine coronavirus highly pathogenic for dogs**. *Emerg Infect Dis* 2006, **12**:492-494.