Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ELSEVIER

Host–microbe interactions: viruses
A never-ending creativity contest

Editorial overview

Adriano Aguzzi

Current Opinion in Microbiology 2004, **7**:397–399

This review comes from a themed issue on
Host–microbe interactions: viruses
Edited by Adriano Aguzzi

Available online 20th July 2004

1369-5274/$ – see front matter

DOI 10.1016/j.mib.2004.06.017

Adriano Aguzzi

Institute of Neuropathology, Department of Pathology, University Hospital of Zürich, Schmelzbergstrasse 12, CH-8091 Zürich, Switzerland
e-mail: Adriano@pathol.unizh.ch

Adriano Aguzzi's research activity focuses entirely on prions, exploring how they damage brain cells, how they reach the brain after entering the body from peripheral sites, and why they accumulate in follicular dendritic cells. In addition to his basic scientific interests, Adriano Aguzzi has developed and patented diagnostics and therapeutics for prion diseases. He is the founder and director of the Swiss National Reference Center for Prion Diseases, and the Chairman of the Department of Pathology at the University Hospital of Zürich. He has been President of the Swiss Society of Neuropathology, and Associate Dean for Research at the University of Zürich Medical School. He received the Gold Medal of the European Molecular Biology Organization 1998, the Ernst-Jung Award 2001, and the Robert-Koch Award 2003. He holds honorary doctorates in Medicine and in Biology bestowed, respectively, by the Universities of Liege and Bologna.

There are many good reasons why the study of viruses has fascinated life scientists for more than a century. On the one hand, the relatively simple makeup of most viruses renders them particularly well tractable by reductionist approaches. Consider, for example, the simple and beautiful geometry of eicosahedral capsids, the interwoven and overlapping reading frames of retroviral genomes, or the highly focused strategies by which oncogenic papova viruses subvert the cell cycle. All of these are examples of very functional – and yet disarmingly minimalist – aspects of viral life. Typically, there is no 'junk DNA' to deal with; every single nucleotide has a precise raison d'être, which can thankfully be analyzed in all due detail by forward or reverse genetics.

But there is another aspect of life as a virus that is a source of continuous amazement: the 'evil intelligence' with which viruses exploit the evolutionary drive towards co-evolution with (or against) their hosts. Most conspicuously in the case of RNA viruses, co-evolution goes along with elaborate conspiracies aimed at shanghaiing the molecular machines of their mammalian hosts for the virus' own benefit.

Besides serving the viruses, this evil intelligence has an upside in that it is exploitable for studying cellular physiology. The bewildering affinity of viral constituents for crucial host cell proteins has taught us a great deal about how cells work. Finally, the virus's weapons are increasingly being put to fruition for good purposes, as for example in the case of lentiviral (and possibly spumaviral) vectors for gene transfer to postmitotic cells.

Of course, the host will attempt to counterstrike in a variety of ways, for example by deactivating the molecular handles exploited by the virus, or by locking onto the virus immunologically. Even the present issue of *Current Opinion in Microbiology* could be regarded as a higher-order antiviral strategy of the human host. This series of state-of-the-art reviews on virus–host interactions strives to disseminate virological knowledge – which in turn may confer a competitive advantage to the human host. The individual articles have been written by leaders of their respective fields, and represent a cross-sectional report on the current state of knowledge for a selection of RNA viruses: foamy viruses, HIV, and the coronavirus responsible for severe acute respiratory syndrome (SARS). The issue is rounded by a discussion of novel concepts in antiviral immunity, and by a synopsis of viruses that elicit psychotropic effects in their hosts.

Foamy viruses continue to be quite mysterious beasts. Originally named after the dramatic cytopathic effects observed on foamy-virus infected cultured cells, they appear to be highly prevalent in non-human primates. Based on the severe neurodegeneration observed in transgenic mice expressing human foamy virus (HFV) regulatory proteins [1], many observers including myself have suspected that HFV may be responsible for neurological diseases of primates [2,3]. However, over the ensuing decade it has not been possible to substantiate this suspicion, and HFV remains a virus in search of a disease [4]. This is – of course – excellent news for the unfortunate zoo technicians who have contracted HFV infection from monkey bites. Besides, that HFV may not be all that neuropathogenic after all, enhances the prospects for the proposal presented by Saib and colleagues that HFV may be used as a vector for gene therapy. Before that prospect can become reality, many issues will need to be ironed out, not least the fact that the function of some of the most abundant gene products of HFV continues to be unknown.

As for Human Immunodeficiency Virus (HIV), the situation mirrors in reverse that of HFV. HIV has developed into one of the most devastating human pandemics of the past century. Like all retroviruses, HIV cultivates an intricate relationship with its host. The review by Trkola leads us through the virus' travel within the host cell, and discusses progress in understanding each step in the viral life cycle. For all the research on the functional significance of HIV gene products, large areas remain nebulous. The biggest mystery, in my opinion, continues to surround the Nef regulatory factor. Although Nef is indispensable for pathogenicity *in vivo* [5], its precise mode of action, its cellular partners, and the relative importance of the many functions ascribed to Nef, are still elusive.

In a very short period of time since its inception, severe acute respiratory syndrome (SARS, discussed by Ziebuhr in this issue) provoked a worldwide health scare. In more than one way, the SARS pandemic epitomizes the new risks arising from the combination of highly infectious emerging pathogens with the limitless exchange and travel in the 'global village'. Alternatively, the SARS epidemic can be viewed as a fantastic success story of modern infectology. The clinical case definition of SARS was identified very quickly, mainly because of the heroic commitment of the late Dr. Carlo Urbani (for an account of Urbani's remarkable work and untimely death, see http://www.aicu.it/carlourbani.asp). A wave of panic arose in South East Asia, and the effects for that region were devastating. The gross domestic product of Taiwan, at the peak of the epidemic, went down to zero – as 170,000 citizens were isolated in an eventually successful effort to contain viral spread. The molecular identity of the SARS coronavirus (SARS-CoV) was established in record time. After some initial problems mainly in South China, the cooperation between scientists and health authorities worked seamlessly and ensured containment of the epidemic. The development of antiviral vaccines is arguably among the most impressive success stories in medicine, and advanced efforts are now underway to produce effective vaccines against SARS-CoV.

Lipkin and Hornig reflect on virus–host interactions from a different prospective, and discuss the impact of viral infections on the human mind. That viruses can be psychotropic is by no means a novel concept: think for example of rabies infection, which has been known to cause 'hydrophobia' since ancient times. The synopsis of Lipkin and Hornig shows that psychotropic effects may represent the rule rather than an exception in viral infections. Certain syndromes are undisputed and extremely well documented: these include the AIDS-dementia syndrome [6] and the devastating and irreversible hippocampal syndromes brought about by Herpes simplex encephalitis. In other diseases, the situation is murkier and sometimes just conjectural. It has been speculated many times that at least some forms of schizophrenia and of major depression may be of viral origin: the equine Borna Disease Virus (BDV), the molecular definition of which Ian Lipkin has contributed significantly [7,8], has surfaced as a candidate pathogen time and time again. However, incontrovertible evidence is still lacking. The authors enumerate the evidence in favor and against each of these arguments, and provide some insight into ongoing (hitherto unpublished) efforts at clarifying some of these possible pathogenetic links.

The life of viruses can only be understood in the context of their hosts' reactions to infection. The most prominent of these reactions is immunity. The traditional view maintained that immunity occurs in two ways: an *adaptive* sophisticated, immensely effective clonal immune response, and an *innate*, brachial and primitive response that provides an approximate and barely functional first line of defense. Needless to say, the discovery of pathogen-associated molecular patterning receptors, such as the rapidly growing family of Toll-like receptors (TLRs) [9], has significantly altered that perception: we now know that the innate immune system is much more sophisticated than had been suspected. The current enthusiasm for TLR immunotherapies (of everything, from pathogens to cancer) may be excessive: TLR stimulation is a potent double-edged sword, and in our own experience chronic administration of TLR agonist can be severely counterproductive [10].

In the final article of this issue of *Current Opinion in Microbiology*, Recher and colleagues (all from the renowned laboratory of Rolf Zinkernagel, whose discovery

of the function of histocompatibility antigens in antiviral defense earned him the Nobel Prize) discuss the functional aspects of humoral immune responses to non-cytopathic RNA viruses. A delicate equilibrium between viral mutagenesis and the induction of broadly specific 'public antibodies' allows for the development of viral escape variants – until the viral quasispecies collapses because of replicational error catastrophe. After describing their elegant analysis of viral–host interplays in the model system of lymphocytic choriomeningitis virus (LCMV), the authors attempt to draw some enticing generalizations. It will be particularly challenging to test their contention that understanding the induction of cross-neutralizing public antibodies will help the development of HIV vaccines.

Acknowledgments

I am primarily indebted to the many students and postdocs who have spent their time in my laboratory over the past decade. My own work on prion biology was kick-started by Charles Weissmann in 1992; we have maintained a lively and productive collaboration to the present day. The mind-boggling expense of running a prion lab is being met by the Cantonal Authorities of Zurich and by many philanthropists; generous and substantial help was recently provided by the Stammbach foundation and by the National Prion Research Program of the US Department of Defense.

References

1. Bothe K, Aguzzi A, Lassmann H, Rethwilm A, Horak I: **Progressive encephalopathy and myopathy in transgenic mice expressing human foamy virus genes**. *Science* 1991, **253**:555-557.
2. Aguzzi A: **The foamy virus family: molecular biology, epidemiology and neuropathology**. *Biochim Biophys Acta* 1993, **1155**:1-24.
3. Aguzzi A, Bothe K, Wagner EF, Rethwilm A, Horak I: **Human foamy virus: an underestimated neuropathogen?** *Brain Pathol* 1992, **2**:61-69.
4. Weiss RA: **Foamy retroviruses. A virus in search of a disease**. *Nature* 1988, **333**:497-498.
5. Kestler HW 3rd, Ringler DJ, Mori K, Panicali DL, Sehgal PK, Daniel MD: **Importance of the nef gene for maintenance of high virus loads and for development of AIDS**. *Cell* 1991, **65**:651-662.
6. Navia BA, Cho ES, Petito CK: **The AIDS dementia complex: II. Neuropathology**. *Ann Neurol* 1986, **19**:525-535.
7. Briese T, Lipkin WI: **Molecular biology of Borna disease virus**. *Curr Top Microbiol Immunol* 1995, **190**:1-16.
8. Hornig M, Briese T: **Borna disease virus**. *J Neurovirol* 2003, **9**:259-273.
9. Coutinho A: **Innate immunity: from lymphocyte mitogens to Toll-like receptors and back**. *Curr Opin Immunol* 2003, **15**:599-602.
10. Heikenwalder M, Polymenidou M, Junt T, Sigurdson C, Wagner H, Akira S, Zinkernagel R, Aguzzi A: **Lymphoid follicle destruction and immunosuppression after repeated CpG oligodeoxynucleotide administration**. *Nat Med* 2004, **10**:187-192.