

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Introductory Chapter: Unconventional Philosophy of Herpesvirus Infections

Joseph Ongrádi

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64818>

The course of herpesvirus infection in human and animals is not so simple as it has been presumed on the analogy of other microbes at the beginning of virology era. Classification into acute and chronic infections, simple distinction of complete clinical and virological recovery or perishing of the host organism belong to the conventional views on the course and outcome of virus infections. But several other forms of existence of herpesviruses (HHVs) in the host are possible. Many diverse interactions between the macro-organism and herpesviruses have been discovered gradually. In spite of these new data, conventionally, the idea about one organism causing one well-characterized disease has remained in the mind of the majority of both many medical, veterinary professionals and the public. Nowadays we believe that we understand the pathomechanism of herpesviral diseases. Simply saying, this is not true, because, frequently we encounter new experimental evidence that cause surprise and continuously modify dogmas. The conventional way of our thinking on host-viral interaction is somewhat static, but the life-long flow of events between invading herpesviruses and the defensive organism is dynamic: several alternative ways on both sides might influence outcome. Furthermore, their bilateral interplay is modified by many intrinsic and extrinsic factors, consequently it is rather multilateral. This moment there are delicate methods to follow post-infection events at the molecular level. Beside structural polypeptides, herpesviruses encode a large number of proteins with enzymatic or regulatory functions. The exact way of regulating their activities by post-translational modifications, e.g. glycosylation or phosphorylation, is hardly explored. Events at sub-molecular level and energy flow during assembly of their structural components are almost unknown. Basic physics, not conventional virology could help supply knowledge in these matters. Data processing by computers analyses tens of thousands of data obtained in one model experiment or clinical cohorts including large number of patients, but in future we have to extrapolate their pathophysiological meaning to clinical relevance. It is surprising at the first glance, that the same herpesvirus species can

contribute to both acute clinical picture exhibiting characteristic symptoms (vesicles, rash, fever, etc.), and chronic, debilitating diseases without apparent virus production (tumours, autoimmune diseases, etc.). Similarly, related herpesviruses could induce the same clinical symptoms, as herpes simplex virus (HSV) 1 and 2, or cytomegalovirus (CMV) and Epstein-Barr virus (EBV), or HHV-6B and HHV-7. These suggest that our detecting systems are not fine enough to distinguish only superficially identical processes. We are on a good path to reveal the importance of genetic background, namely, polymorphism of both the virus and its host in the course of pathogenesis. Latency, persistence can be regarded as a balanced state between herpesviruses and animals. Instead of complete gene expression and virion production, partial gene expression evolved through phylogenesis and co-evolution by the host and its herpesviruses. Even maintenance of episomal latency of herpesviruses is not a passive process, it requires active viral gene expression as it has been shown in the case of Epstein-Barr virus and herpes simplex virus. Partial gene expression was described in EBV-associated or Kaposi sarcoma herpesvirus (KSHV)-associated tumours several decades ago. Both life-long latency without activation and malignant transformation of cells and consequent contribution to tumour induction and progression are a dead end for the virus along with the perishing host instead of replication and spreading to the environment to find new hosts. Another unusual aspect of herpesvirus pathogenicity is that in 0.2–0.85% of the human population HHV-6A and HHV-6B are integrated in the telomeric region of human chromosomes, and transmitted vertically by standard Mendelian inheritance or by any cell donation [1]. The time and mode of integration in our ancestors are unknown. Some of the carrier persons suffer from neurological symptoms for several years with remittances and relapses [2]. At this moment it is not known whether the life span is modified by HHV-6 species. In combatting defence mechanisms of the organism, different herpesviruses developed cascade mechanisms to mimic several molecular events hijacked from their host. Among alternative infection strategies these are regarded as parts of immune evasion. Can we introduce similar or other human host genes into herpesvirus vaccines to improve their efficacy? Can we introduce genes of animal origin into a human or animal herpesvirus vaccine? Would it be dangerous or unethical? How to select a human gene donor? There are attempts to use HHV-7 as a vector to treat genetic disorders, because this virus has been regarded as ubiquitous and harmless. But lately several clinical reports have shown that it reactivates in the recipients after solid organ transplantation and aggravates CMV disease. In bone marrow or stem cell transplant recipients, usually in small children with leukemias, it also reactivates, and can elicit a very severe, frequently lethal encephalitis. Delayed primary HHV-7 infection in adults might result in a generalized infection, tetraplegia and encephalitis [3]. Conventional common belief about HHV-7 has been turned to the opposite direction in a few years of time.

To find new host cells, cell-to-cell spread is a convenient way. Some herpesviruses are regarded as cell associated, but the exact molecular cascade in this process has not been elucidated yet. So far, we have known that alteration of the function of neighbouring cells or distant cells is mediated by soluble mediators, cytokines and chemokines. Discovery of micro-vesicles and exosomes that can contain fragments of viral nucleic acid, mRNAs and microRNAs with regulatory potential will change our ideas about the regulation of the whole body of a macro-organism by viruses. These vesicles are released from infected cells to the microenvironment or

the circulation, and are taken up by another cells in the vicinity or very far in the body, subsequently they induce further pathological changes that have not directly been credited with virus infections so far. Accumulating evidence suggests that this mechanism is widely used by human herpesvirus species. Exosomes released from HSV-1-infected cells can contain viral polypeptides (gH, gD). Interestingly, they contain modified tegument and envelope proteins that usually originate from the light particles of HSV. Tegument proteins outside the nucleocapsid exert very important regulatory functions. Such content of exosomes promote spread and latency by HSVs. CMV-infected cells release exosomes with cellular molecules that are necessary for virus uptake. These might contribute to allograft rejection in transplant recipients. Exosomes released from HHV-6-infected cells transfer MHC I molecules in addition to complete viral particles. This latter is an absolute viral journey in disguise throughout the whole body, even crossing the blood-brain barrier. Furthermore, growth factors that are very important in EBV pathogenesis can be shuttled into exosomes. Viral antigens in the absence of apparent EBV replication can be transferred to other cells, consequently they can induce autoimmune or other diseases. Exosomes produced by KSHV-infected cells can carry both cellular and viral mRNAs promoting sarcoma metastases. All these phenomena contribute to the transient infection, a newly recognized form of viral existence in the body (see references in [4]).

The structure of herpesviruses comprising the nucleocapsid, tegument and envelope resembles the cellular nucleus, cytoplasm and cell membrane, respectively [5]. The regular belief is that the effect of viruses on cells starts when virus genes are expressed in the cells. Really, this effect starts much earlier, when virions attach to receptors and co-receptors instructing them to send fake messages to reprogram cellular machinery.

Asymptomatic virus shedding is very common in all herpesvirus infections. At the population level, it can be difficult to establish the source and time of infection, e.g. in contract tracing, to find and prove the possible donor in certain cases, even in the court, decades later, or to describe viral epidemiology. Simultaneous herpesvirus infections, or in the presence of one species in the body, a super-infection by another herpesvirus species might occur. In such events, direct interaction in the same host cells or indirect interaction between different cells infected by distinct viruses can take place, resulting in intracellular or trans-cellular transactivation between two competent viruses. Interactions among herpesviruses promote reactivation from latency, profoundly modify innate immunity and T-cell activity, only a few facts to mention [6]. Interaction of herpesviruses with other viruses has gained clinical importance lately, especially in AIDS patients. All human herpesvirus species are involved in the one way or mutual transactivation with HIV facilitating AIDS progression. Especially β - and γ -herpesviruses are able to transactivate other unrelated viruses, bacteria and parasites [7]. The net effect of transactivation is neither additive nor synergistic; new formulas have to be created for their mathematical modelling. It is conceivable that formulas will depend on actual virus pairs. These phenomena listed above could be regarded as crossroads of epidemiology: the unknown source and time of infection by the participating viruses pose a nightmare to classical epidemiologists.

The simplest question is: do animals including human contain a normal virus flora similarly to the normal bacterial flora? Latency, persistence of herpesviruses with asymptomatic

shedding but without apparent harm to the host might suggest an answer: yes [6]. But appearance of clinical symptoms, tumours, even causing acute lethal complications by the same reactivated viruses imply no. No sharp distinction, a clear answer can be made regarding our virome. It is important for human to undergo several bacterial infections during the early period of our life cycle: some microbes establish the normal flora and all of them induce some form of immunity (e.g. systemic, mucosal). Their presence in the body and wide range effects significantly exceeds these simple facts. It seems that it is also important to acquire herpesvirus infections in early childhood. These infections are usually asymptomatic or mild conferring protection against super-infection. Delayed primary herpesvirus infections of seronegative individuals usually are accompanied by severe clinical manifestations. The order of sequential primary infections could be regulated. A simple example is shown by HSV-1 infection in infants, HSV-2 infection in adolescents or HHV-6B infection around 6 months of age, HHV-7 infection around 3 or 4 years of age in spite of the same, salivary route of transmission. The exact mode of regulation is absolutely unknown. Unfortunately, rapidly changing life style and other social factors not only disturb but disrupt these well established, conserved biological processes [3].

Herpesviruses easily adapted themselves to different animals, and through co-evolution with the given host an equilibrium has established for the compromise of both partners. The interaction is very intimate and varies by both herpesvirus species and the host macro-organism. That is one of the reasons why studies on herpesvirus pathogenesis has been hindered by the lack of appropriate animal models, and this is especially true for β -herpesvirinae and γ -herpesvirinae.

From these examples taken arbitrarily, it is conceivable that herpesviruses must not be regarded as conventional parasites, their existence in the body is neither mutualism nor commensalism, rather it is challenging to regard them as unconventional pathogens.

Author details

Joseph Ongrádi

Address all correspondence to: ongradi.jozsef@med.semmelweis-univ.hu

Institute of Medical Microbiology, Semmelweis University, Budapest, Hungary

References

- [1] Morisette G, Flamand L: Herpesviruses and chromosomal integration. *J. Virol.* 2010; 84:12100–12109. DOI: 10.1128/JVI.01169-10

- [2] Montoya JG, Neely MN, Gupta S, Lunn MR, Loomis KS, Prichett JC, Polsky B, Medveczky PG: Antiviral therapy of two patients with chromosomally-integrated human herpesvirus-6A presenting with cognitive dysfunction. *J. Clin. Virol.* 2012; 55:40–45. DOI: 10.1016/j.jcv.2012.05.016
- [3] Ongrádi J, Stercz B, Kövesdi V, Nagy K, Prichett J, Ablashi D, Jacobson S: Human herpesvirus 6A, 6B, and 7 encephalitis. In: Singh SK, Ruzek D, editors. *Neuroviral infections*. Boca Raton, FL: Taylor & Francis Group/CRC Press; 2013. pp. 313–345. ISBN: 978-1-46-656719-1
- [4] Anderson MR, Kashanchi F, Jacobson S: Exosomes in viral disease. *Neurotherapeutics*. 20 June, 2016. DOI: 10.1007/s13311-016-0450-6. Epub ahead of print.
- [5] Brown N, Bhella D: Are viruses alive? *Microbiol. Today*. 2016; 43:58–61. www.microbiologysociety.org
- [6] Reese TA: Coinfections: another variable in the herpesvirus latency—reactivation dynamic. *J. Virol.* 2016; 90:5534–5537. DOI: 10.1128/JVI.01865-15
- [7] Ongrádi J, Kövesdi V, Nagy K, Matteoli B, Ceccherini-Nelli L, Ablashi DV: *In vitro* and *in vivo* transactivation of HIV by HHV-6. In: Chang TL, editor. *HIV-host interactions*. Vienna, Austria: InTech; 2011. pp. 257–298. ISBN: 978-953-307-442-9

