Trends in Microbiology

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Review

Herpesviruses and Their Host Cells: A Successful Liaison

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During a long history of coevolution, herpesviruses have reached a fine-tuned balance with their hosts, allowing them to successfully persist and spread to new hosts without causing too much damage. Only under certain circumstances, as in neonates or immunocompromised individuals, they may cause serious diseases. The delicate balance between herpesviruses and their hosts results from interactions of a great variety of viral and cellular factors which together shape the tropism for a particular host, tissue, or cell. Understanding these interactions will provide insight into the viral life cycle and cell biology in general. Moreover, it will also facilitate comprehension of herpesvirus pathogenesis, enabling the development of new strategies to combat herpesviruses in cases where they cause disease.

Herpesviruses: A Strategy of 'Travel and Hide'

Primary herpesvirus infection generally results in a productive infection which is subsequently limited by the host immune response, leaving behind latently infected cells which persist in the host [1]. Latency can be defined as carriage of the virus genome in the absence of virus production but the ability of the virus to reactivate and to re-enter the lytic cycle. During latency, only restricted sets of viral genes are expressed and the viral genomes mostly persist as episomes in the nuclei of infected cells. In some cases, viral genomes can also integrate into the host genome.

During their life cycle, herpesviruses usually infect different cell types in various tissues. Subclassification of herpesviruses is partially based on their cell and tissue **tropism** (see Glossary). α-Herpesviruses, such as herpes simplex virus (HSV) or varicella zoster virus (VZV), become latent in cells of the nervous system. β-Herpesviruses, including human cytomegalovirus (HCMV), are characterized by a very broad cell tropism when productively infecting cells and become latent in progenitors of the hematopoietic cell system. γ-Herpesviruses, such as Epstein–Barr virus (EBV) or Kaposi sarcoma-associated herpesvirus (KSHV), show a more restricted cell tropism and are characterized by their ability to transform latently infected cells and induce tumors in their infected hosts.

Usually, the portal of entry for a specific herpesvirus is not the site of latency. Thus, the incoming virus has to travel to the site of latency using either migrating cells as vehicles for dissemination or, in the case of α-herpesviruses, cell protrusions of nerve cells. Often, reactivating virus also uses the same routes back to ensure horizontal spread from productively infected cells. Understanding the interplay of viral and host cell factors during the different phases of the viral life cycle will not only provide insights into disease pathogenesis but also be the basis for the development of new antiviral drugs and herpesvirus-based vaccine or gene-therapy vectors. For these reasons, herpesvirus infection of different cell and tissue types is an area of intensive research using established and new techniques or screening methods (Table 1).

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Herpesvirus host cells are defined by their susceptibility to productive or latent infection.

Herpesvirus host cells contribute to navigation of viruses through the infected host, either directly as vehicles or indirectly by shaping the glycoprotein content of viral envelopes.

Herpesviruses can manipulate their host cells by changing their differentiation status.

Herpesviruses stand out by a highly redundant equipment with regulatory proteins or noncoding RNAs. This redundancy stands in the way of clearing a herpesvirus infection.

The development of new antiherpesviral drugs or vaccines, and the application of herpesviruses as oncolytic agents, vaccine- or gene-therapy vectors depends on understanding interactions between viral and host cell factors.

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Table 1. Methods and Techniques Used to Study the Interaction of Viral and Host Factors

Methods	Selected Applications	Refs
Computational biology approaches	Generation of integrated networks for virus (KSHV)–host interactions analysing sequence-based functional annotation and expression, RNAi- and experimental data	[58]
Classical loss of function/gain of function analyses	Determination of the role of THY-1 in HCMV infection via downregulation, antibody block, knockout and overexpression	[59]
Classical protein–protein interaction analyses like yeast two hybrid screens	Identification of cellular interaction partners of HSV-1 proteins by a genome-wide virus–host protein interaction screen	[60]
Integrative genome-wide approaches like high-throughput **RNAi** screens	Investigation of the functional role of cellular proteins in HSV-1 replication via siRNA-mediated depletion of host factors	[60,61]
Comprehensive **proteomic** analyses like **SILAC**-based quantitative proteomics	Global phosphorylation patterns in signaling pathways modulated by the EBV protein kinase BGLF4	[62]
Mass-Spec-based proteomics	Identification of an interaction between HSV-1 ICP0 and the cellular protein RanBP10 by **tandem affinity purification (TAP)** and **mass spectrometry**	[63]
Quantitative temporal viromics	Systematic quantitative analysis of temporal changes in host and viral proteins during HCMV infection by multiplexed tandem-mass-tag-based mass spectrometry	[64]
Subcellular fractionation combined with quantitative proteomics	Identification of Hsp70 isoforms as constituents of the KSHV replication and transcription compartments (RTCs)	[65]
Single-cell mass cytometry (CyTOF)	Analysis of concurrent changes in multiple host cell factors at the single cell level to follow phenotypic remodeling of T cells infected with VZV	[9]
High-resolution chromatin immunoprecipitation and deep sequencing (ChIP-Seq)	Analysis of protein–DNA interactions by combining chromatin immunoprecipitation with next-generation DNA sequencing to analyze the dynamic changes in CTCF and cohesin binding during KSHV reactivation	[28]
cre/*loxP*-system	Tracking MCMV and MHV-68 host cells *in vivo* by infecting mice cell type-specifically expressing Cre-recombinase with floxed reporter viruses or by infecting mice carrying floxed cellular genes with Cre-expressing viruses	[33,66]

Herpesvirus Tropism: Factors Influencing Herpesvirus Infection of Different Cell and Tissue Types

An important concept for understanding the mechanisms of infection of different cell and tissue types is the concept of tropism. This concept has been comprehensively reviewed by Heise and Virgin [2]. Briefly, tropism is the capacity of a virus to infect specific cells, tissues or species, and is determined by both susceptibility and permissiveness. A host cell is susceptible if it has the proper receptor(s), allowing the virus to enter the cell, and it is permissive if it allows viral replication, that is, it supports productive infection. Thus, tropism is determined by many factors of both the virus and the host. Although essential for infection, passage through the cellular membrane barrier is just the first step to successful infection. Several events that occur after binding and entry exert profound effects on the further progress of the infection. For example, the host cell is armed with molecules which can directly inhibit viral replication, induce antiviral innate

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