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Insights into chronic gamma-herpesvirus infections

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Herpesviruses are among the most ubiquitous and successful viruses known, and are thought to have co-evolved with their vertebrate hosts during speciation. Indeed, many of the herpesviruses exhibit very restricted host tropism, suggesting that they have become highly adapted to their host. A notable feature of all known herpesviruses is their ability to chronically infect their host — alternating between cycles of virus replication and latent infection. With few exceptions, herpesviruses fall into one of 3 distinct families — alpha-herpesviruses, beta-herpesviruses or gamma-herpesviruses. This issue will focus on our current understanding of chronic gamma-herpesviruses infections (with one exception, the final review by Mocarski and colleagues which reviews manipulation of host cell death pathways by the beta-herpesvirus, cytomegalovirus). The gamma-herpesviruses are lymphotropic viruses that, unlike the alpha-herpesviruses and beta-herpesviruses, are oncogenic — consistently associated with the development of lymphoproliferative diseases and lymphomas (as well as other cancers) in a subset of infected individuals. There are two gamma-herpesviruses that are known to infect humans, Epstein–Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV). EBV was discovered from its tight association with the endemic form of Burkitt's lymphoma. It has subsequently been shown to be involved in the genesis of another geographically restricted cancer, nasopharyngeal carcinoma, as well as a subset of Hodgkin's lymphoma and gastric carcinoma. Similarly, KSHV was discovered through its tight association with Kaposi's sarcoma and has subsequently been shown to be the etiologic agent of primary effusion lymphoma (PEL) and Castleman's disease.

Both EBV and KSHV have a very narrow host range, and this has hampered *in vivo* studies. However, over the past 20 years there has been significant progress developing alternative animal models — particularly using nonhuman primate models of gamma-herpesvirus pathogenesis. Thus, we have included in this compilation reviews focused on the human viruses, as well as studies in animal models. Thorley-Lawson *et al.* review the germinal center B cell model of EBV infection, which postulates that EBV infection and manipulation of the germinal center reaction drives EBV infection into the memory B cell compartment. This is an attractive model because: first, it accounts for the known ability of EBV to manipulate B cell proliferation and differentiation — aspects of which can be observed upon virus infection of naïve B cells in tissue culture; and second, establishment of virus infection

in memory B cells provides a long lived reservoir in which EBV can persist in the absence of detection by the host immune system. The authors also discuss recent mathematical modeling studies that argue in favor of a model in which virus reactivation and new infection plays a prominent role in the maintenance of chronic infection. Presumably many of the questions raised by the mathematical modeling of EBV infection in humans can be addressed using the closely related rhesus lymphocryptovirus (rhLCV). Wang describes the current state of the rhLCV model, along with discussion of a New World lymphocryptovirus that infects cotton-top tamarins.

While EBV is a member of the γ 1-herpesvirus (lymphocryptovirus) family, KSHV is member of the γ 2-herpesvirus (rhadinovirus) family. Rhadinoviruses appear to be wide spread among vertebrate species, but lymphocryptoviruses have only been found in primate species. Alignment of sequenced lymphocryptovirus and rhadinovirus genomes reveals significant overall conservation of genome organization — in particular, those genes involved in virus replication are well conserved. However, genes known to be involved in aspects of latent infection are, by in large, not obviously conserved between lymphocryptoviruses and rhadinoviruses [although many of these nonconserved latency genes share common functions (e.g., EBV EBNA1 and KSHV LANA)]. A comprehensive overview of KSHV pathogenesis is provided by Dittmer and Damania, which is followed by a review of diseases associated with the closely related rhesus macaque rhadinovirus (RRV) by Estep and Wong.

A central issue since the discovery of gamma-herpesviruses has been how these viruses differentially regulate viral gene expression during latent infection vs virus replication. Paul Lieberman provides a detailed overview of epigenetic regulation of EBV and KSHV latency — including the complex cast of viral and cellular factors involved. One of the important epigenetic marks found in gamma-herpesvirus genomes is DNA methylation. Indeed, a notable feature of gamma-herpesviruses is that their genomes exhibit significant CpG suppression, indicating that over their evolution they have been extensively subjected to DNA methylation. This has been most clearly worked out for EBV infection, where both *in vitro* and *in vivo* extensive methylation of the viral genome has been observed. For example, in Burkitt's lymphoma (BL) tumors the EBV genome is extensively methylated and viral protein expression is restricted to the episome maintenance protein EBNA1. Treatment of BL cell lines with 5-azacytidine can reverse viral genome methylation and results in re-expression of the full complement of EBV latency-associated gene expression. That methylation of the viral genome in BL tumors reflects a normal aspect of EBV biology *in vivo* has been shown by examining the state of the viral genome in healthy seropositive individuals. In the review by Woellmer and Hammerschmidt, they discuss recent work demonstrating that host-cell driven methylation of the viral genome plays a central role in both the establishment of viral latency in B cells as well as virus reactivation from latency. The model they propose suggests that EBV exploits host cell methylation — normally a potent host cell defense mechanism against intracellular pathogens — to regulate the EBV life cycle.

The role of miRNAs in herpesvirus pathogenesis is an area of intense interest, and it has become clear that these noncoding RNAs can play a central role in viral pathogenesis and

tumor development. Ying *et al.* review our current understanding of the role of these viral miRNAs in KSHV and EBV infection. In addition, next generation sequencing approaches are providing new insights into the complexity of herpesvirus gene expression. Krug provides an overview of how RNAseq analyses are altering our view of gamma-herpesvirus gene expression.

An important aspect of those viruses that can chronically infect their host, is the ability of these viruses to avoid detection and clearance by the host immune response. Gamma-herpesviruses are no exception, employing a plethora of strategies to evade both innate and adaptive host responses. A comprehensive review of this field is provided by Feng *et al.* As discussed in this review, evasion of host cell death pathways is an important aspect of gamma-herpesvirus pathogenesis. The final review, by Kaiser *et al.*, describes recent work documenting the importance of murine cytomegalovirus interference with host cell programmed necrosis. The latter studies have defined a previously unappreciated role of caspase 8 in regulating not only extrinsic apoptosis, but also RIP3-mediated programmed necrosis. Whether gamma-herpesviruses manipulate programmed necrosis is currently unknown.

In summary, as life-long ‘passengers’ in their infected hosts, herpesviruses must strike a delicate balance with the host immune response. To achieve this, γ -herpesviruses devote multiple strategies and resources to manipulate the key signaling pathways described here, ultimately promoting the survival of virus infected cells, immune evasion and tumorigenesis. Moreover, the high frequency of molecular piracy by γ -herpesviruses allows researchers to study these viral mimics and gain insights into the mechanisms viruses use to divert cellular pathways, even leading to the discovery of new classes of cellular proteins and miRNAs.

Biographies

Dr. Jae U. Jung is a Fletcher Jones Foundation Professor, Hastings Foundation Professor, Distinguished Professor and Chair of the Molecular Microbiology and Immunology at the Keck School of Medicine of USC and a director of USC Emerging Pathogens and Immune Diseases Institute. He has made major contributions to the fields of gamma-2 herpesvirus pathogenesis and virus–host interaction: first, the identification of human Kaposi's sarcoma associated herpesvirus oncogenes and IFN evasion mechanisms of viral interferon regulatory factors; second, the inhibition of T lymphocyte-mediated and natural killer cell-mediated cytotoxicity by herpesvirus E3 ligases and the identification of viral anti-apoptosis and anti-autophagy pathways; and third, the development of a new infectious herpesvirus genetic clone and animal model. Using the genetic manipulation of viral genome and animal models, his lab investigates viral epigenetic regulation, gene expression, persistence, pathogenesis, and vaccine development.

Prof. Samuel Speck is Georgia Research Alliance Eminent Scholar in Molecular Pathogenesis, and Professor in the Department of Microbiology and Immunology at Emory University School of Medicine in Atlanta. Sam's research group studies two gamma-herpesviruses, Epstein–Barr virus (EBV) and murine gammaherpesvirus 68 (MHV68), focusing on understanding: first, how these viruses regulate viral gene expression during

latency; second, how they modulate and avoid the host immune response; and third, how they switch from a latent infection to replication of the viral genome, a process that is essential for propagation of these viruses to uninfected individuals. As a postdoctoral fellow Sam was the first to show that the EBV EBNA gene transcripts arise from a primary transcriptional unit that spans nearly 100 kbp of the viral genome. Because of the narrow host tropism of EBV and KSHV, Sam's recent research has focused primarily on the highly tractable MHV68-mouse infection model. Using viral genetics, coupled with available knockout and transgenic mouse strains, his lab continues to address basic issues of how chronic gamma-herpesviruses infections are established and maintained.