Aspects of Human Cytomegalovirus Latency and Reactivation

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Abstract Primary infection of healthy individuals with human cytomegalovirus (HCMV) is usually asymptomatic and results in the establishment of a lifelong latent infection of the host. Although no overt HCMV disease is observed in healthy carriers, due to effective immune control, severe clinical symptoms associated with HCMV reactivation are observed in immunocompromised transplant patients and HIV sufferers. Work from a number of laboratories has identified the myeloid lineage as one important site for HCMV latency and reactivation and thus has been the subject of extensive study. Attempts to elucidate the mechanisms controlling viral latency have shown that cellular transcription factors and histone proteins influence HCMV gene expression profoundly and that the type of cellular environment virus encounters upon infection may have a critical role in determining a lytic or latent infection and subsequent reactivation from latency. Furthermore, the identification of a number of viral gene products expressed during latent infection suggests a more active role for HCMV during latency. Defining the role of these viral proteins in latently infected cells will be important for our full understanding of HCMV latency and reactivation in vivo.
Introduction

The ability of human cytomegalovirus (HCMV), like all herpes viruses, to establish a lifelong persistent infection plays a crucial role in the long-term carriage of this opportunistic pathogen in the human host. It is likely that HCMV persistence, in vivo, involves sites in the host which continually produce low levels of virus. However, it is now clear that it also involves sites which carry the viral genome latently in the absence of any productive infection.

Although HCMV causes few overt symptoms following primary infection of healthy individuals, significant morbidity and mortality is observed in the immunonaive, immunocompromised and immunosuppressed (Ho 1990; Zaia 1990). Primary infection is an important factor in HCMV-mediated disease (see the chapter by W. Britt, this volume), particularly following congenital infection (Griffiths and Walter 2005). However, reactivation from latency is a major cause of disease in certain transplant patients (both solid organ and bone marrow transplantation) and also in late-stage HIV patients suffering from AIDS (Adler 1983; Rubin 1990; Sissons and Carmichael 2002). Consequently, developing an understanding of the mechanisms that regulate latency and reactivation in vivo is of paramount importance for future clinical intervention.

In order to do this, a number of fundamental questions about the basic biology of HCMV need to be addressed: Firstly, in which cells does the latent virus reside? Secondly, in which cells does the virus reactivate. Thirdly, what regulates this latency and reactivation?

The ability to detect latent HCMV, particularly prior to the development of highly sensitive techniques such as the polymerase chain reaction (PCR), is in contrast to the ease of detecting productive HCMV infection during disease. Acute HCMV infection is manifest in numerous tissues (Rubin 1990; Sissons and Carmichael 2002). Epithelial, endothelial, smooth muscle, stromal, fibroblast and neuronal cells all support lytic HCMV replication in vivo (Sinzger et al. 1995; Plachter et al. 1996; see the chapter by C. Sinzger et al., this volume) and, consequently, HCMV pathology can be seen in a diverse range of organs throughout the body. In contrast, HCMV latency appears to be restricted to subpopulations of cell types.

Latency, Carriage and Reactivation of HCMV in the Cells of the Myeloid Lineage

Some of the first instructive observations regarding HCMV latency came from clinical studies. Although it was extremely difficult to detect infectious virus in the blood of normal healthy individuals, it was evident that blood transfusions from healthy sero-positive donors often resulted in the transmission of HCMV to blood donor recipients (Adler 1983). However, the incidence of this transmission was significantly reduced if leukocyte-depleted blood products were used (Yeager et al. 1981; Tolpin et al.