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Herpesviruses pursue strategies to avoid immune detection and establish lifelong latency. Alphaherpesviruses, such as HSV-1, infect humans via keratinized epithelium and set up latency in sensory neurons, providing lifelong residence in an immune privileged site. In contrast, gammaherpesviruses and betaherpesviruses initiate a systemic infection and deal with the host immune response by elaborating immunomodulators that deflect host defense. The gammaherpesvirus EBV gains access to naive B lymphocytes via tonsil epithelium, immortalizing these cells in a memory-like state for life. CMV replicates systemically after infecting via the mucosa, targeting diverse epithelial, endothelial, fibroblast, myeloid, and sometimes glial cells, establishing long-term residence in bone marrow-derived progenitors of dendritic cells (DCs) and macrophages (1). Sporadic/persistent shedding in body fluids is common, ensuring widespread dissemination, such that a majority of the world’s population becomes infected with CMV and other human herpesviruses. CMV is one of the few herpesviruses transmitted across the placenta during pregnancy, resulting in congenital disease. Reactivation of latent virus contributes to CMV disease in the immunocompromised host following hematopoietic or solid organ transplantation, and it is recognized as one source of virus transmission during pregnancy (2). The crucial aspects of the stand-off between human CMV and its host are highlighted by the report in PNAS from Mason et al. (3), where the influence of latent infection over secreted cellular cytokines and regulation of CD4+ T-cell activity is brought front and center.

Models of Cytomegalovirus Latency

Cell culture models have reinforced the role of the cellular differentiation state in the maintenance of CMV latency-reactivation balance. Recent years have seen a focus on the role of the cellular environment in dictating outcome. Only a small proportion (10^-4 to 10^-5) of total bone marrow-derived myelomonocytic cells naturally support CMV latency (4); thus, these models are critical to provide clues into natural persistence and latency (5–10). Precursors of DCs harbor latent infection, and once terminally differentiated into mature antigen-presenting cells, they support reactivation and viral persistent replication (11, 12). Furthermore, the differentiation pathways that lead to reactivation depend on the inflammatory environment and also likely stimulate the adaptive T-cell response to viral infection. The virus confronts the host by corralling and constraining the effectiveness of the cellular antiviral immune response. Healthy individuals mount an extraordinarily broad and sustained antiviral T-cell response, often with 10% or more of total circulating CD4+ and CD8+ T cells being CMV-specific (13). This remarkable T-cell response inflates throughout life, and it may preoccupy the immune system and prevent efficient responses to other pathogens in old age (14). Despite this intense antiviral T-cell response, and despite latent infection being established and maintained in immune cells of the myeloid lineage, CMV is never completely cleared.

Immune Modulation During Latency

Such a complex relationship spawned the search for CMV gene expression and modulators of host defense pathways elaborated during latency (15). Initial microarray-based analyses suggested alterations in immune and other host defense functions that may be regulated by secreted gene products (16). This led to the discovery that virus-encoded IL-10 is secreted during latency and most likely reduces the effectiveness of CD4+ T-cell immune surveillance (17). The recognition that host-encoded chemokine MCP1 (CCL2) is secreted during latency to increase monocyte chemotaxis demonstrates the influence of virus on monocyte behavior (18). This growing understanding predicted that the impact of CMV latent infection extends beyond the infected cell to include the extracellular environment surrounding sites of latency.

The study by Mason et al. (3) builds a more comprehensive picture of the secretome, using a CD34+ hematopoietic stem cell model and a series of carefully assembled controls, including evaluation of virus particle impact on myeloid cells. A viral strategy to undermine cytotoxic CD4+ T-cell activity stands out in this work. Although the cytotoxic potential of MHC class II-restricted CD4+ T cells is less recognized than that of MHC class I-restricted CD8+ T cells, such activity has been frequently detected (19–21). Evidence of a microenvironment around latently infected cells that is specifically immunosuppressive for CD4+ T cells suggests that novel host defense mechanisms may control virus in this unique setting. Two major issues remain: (i) whether other major components of the host defense, such as natural killer or CD8+ T cells, are also modulated during latency and (ii) how latency-associated viral gene products exert control over the latent secretome.

This report (3) also highlights the role of human (h)IL-10, which adds to previous studies that focused on virus-encoded IL-10 expressed during latency (17, 22–24). On the one hand, viral IL-10 may induce hIL-10. An isoform of viral IL-10, cmvIL-10, has the capacity to increase hIL-10 production and modestly increase hIL-10 receptor levels on B lymphoblasts in culture (25). If similar events occur during natural latency, this viral cytokine may drive the latent secretome by up-regulation of hIL-10 and/or hIL-10 receptor levels. On the other hand, additional latent gene products may be at play here. This is another area where additional evidence is needed.

Due to the extreme specificity of CMV, the study of latency has necessitated the development of human cell culture model systems. The system used by Mason et al. (3) employs a primary human hematopoietic stem cell system that has...
provided many insights into establishment, maintenance, and reactivation (11, 26). A major challenge facing this field is validation of model systems. This particular approach has certainly shown promise. Despite these insights, results presented by Mason and colleagues (3) cannot be directly translated to the natural latent infection setting: they must inspire targeted studies to examine mechanisms underpinning latency in naturally infected individuals as well as better understanding of the mechanism underlying reactivation and persistent infection in various myeloid lineage cells.

Ultimately, Mason et al. (3) have added important insights into the immunomodulatory strategies that directly influence the quality and quantity of the host response to infection. This pathogen–host stand-off is initiated at many levels from the time that CMV initially infects a host and continues into latency.