Cytomegalovirus: pathogen, paradigm, and puzzle

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Human cytomegalovirus (CMV), one of the eight herpesviruses that commonly infect humans, is best known for its propensity to cause disease in immunocompromised patients, especially transplant recipients, patients with advanced AIDS, and congenitally infected newborns. Advances in molecular virology coupled with improvements in diagnostic methods and treatment options have vastly improved our understanding of and ability to manage CMV, but many uncertainties remain, including the mechanisms of persistence and pathogenesis and its hypothesized roles in a variety of human illnesses. Here we review recent advances that are reshaping our view and approach to this fascinating virus.

A century of progress

Human CMV infection is extremely common. A recent analysis in the United States revealed an overall 50% seroprevalence among adults (1), but rates in some populations are even higher. For example, approximately 90% of Mexican-Americans in the United States are seropositive by age 50, as are 88% of stem cell transplant patients in Italy and 96% of individuals in southern Brazil (1–4). Despite its high worldwide prevalence, CMV infections are generally asymptomatic, except in newborns and immunocompromised individuals, for whom they can cause life-threatening disease affecting many organ systems.

The virus was first detected in newborns during the early 20th century, when multiple reports described large cells in the urine of children with an often fatal systemic infection referred to as cytomegalic inclusion disease (5). The midcentury development of cell culture methods enabled propagation of CMV, but its detection in clinical specimens often required weeks of cultivation. Rapid diagnostic testing by centrifugation-enhanced incoction combined with detection of CMV antigens in the 1980s was a transforming advance, enabling the diagnosis of CMV to be made in a clinically useful time frame (6). The emergence of effective antivirals in the 1990s was opportune, as CMV-associated disease was increasing in parallel with the AIDS epidemic and use of solid organ transplantation (SOT) and HSC transplantation (HCT). During the past two decades, further advances in diagnosis and treatment have greatly improved our ability to control CMV disease, but the virus still accounts for substantial morbidity, mortality, and cost.

Along with these clinical advances, remarkable progress has been made in understanding the molecular biology of CMV. Application of the nucleic acid and protein analytic methods led to an appreciation of the extraordinary complexity of CMV, a point solidified by the landmark report of the first complete sequence of a CMV strain in 1990 (7). Refinements to methods for studying CMV gene function have continued to reveal myriad mechanisms underlying CMV’s evolutionary success. However, understanding the pathogenesis of CMV diseases remains an enormous challenge, in large part because the virus only grows in human cells and it differs substantially from even its primate-infecting cousins (8–10).

Here we summarize the current understanding of CMV biology and disease. The topic is too broad to cover completely in this format, so the interested reader may wish to consult more comprehensive reviews (11, 12), as well as new reports that are certain to appear in the months and years ahead.

CMV replication: insights but limitations from the lab

Human CMV is the prototypic member of the β herpesvirus subfamily, which also includes human herpes viruses 6 and 7 and many animal CMVs. Its DNA genome is approximately 230 kb in size, the largest among known human viruses, and consists of unique long (UL) and unique short (US) segments, each of which is flanked by inverted repeats (RL and RS; Figure 1). Most of the approximately 200 genes encode proteins, but some express only noncoding RNAs, including approximately 14 microRNAs (miRNAs; refs. 13–15). The central portion of the UL region contains clusters of core genes that have homologs in other herpesviruses, such as DNA polymerase, glycoprotein B (gB), and glycoprotein H (gH), whereas the remainder of the genome contain genes primarily found only in β herpesviruses or unique to human CMV (16, 17). In fact, considerable variation has been detected even among human CMV isolates (18). By convention, CMV genes are named by their position within the genome, although some also have additional descriptive names. For example, UL54 (the 54th gene in the UL region, according to the original report of the CMV, strain AD169, sequence; ref. 7) is the DNA polymerase gene.

Propagation of CMV in cell culture has been an essential research tool but has definite limitations, in part because passage in the laboratory selects for mutants adapted for growth in this unnatural setting (19). As a result, commonly used lab strains have multiple mutations, deletions, and rearrangements (20). For example, the end of the UL region in isolates of the lab strains Towne and AD169 lacks approximately 13 kb of DNA, encoding 19 genes that are present in the Toledo strain (21, 22). Remarkably, inactivating mutations in the RL13 gene are detectable by sequence analyses of the viral genome immediately upon propagation of virus in cell culture (23), which suggests that this gene is necessary for success of the virus in humans but strongly inhibitory to replication in cell culture. The fact that most, if not all, prior laboratory-based studies have used only RL13 mutant viruses reinforces the importance of confirming results of laboratory studies with observations from the clinic. Advances in sequencing technology are sure to improve our understanding of the genetic variation of CMV without confounding artifacts that arise from propagation in the laboratory.

Among the important recent advances has been the characterization of a previously unrecognized CMV entry pathway. Most labo-
However, in infected humans, CMV is commonly found receptors including integrins and possibly growth factor receptors in endothelial cells, epithelial cells, smooth muscle cells, and some one or more of these genes, resulting in their failure to replicate in virion glycoproteins (gB, gH, and gL; Figure 1) with cell membrane and requires the UL128, UL130, and UL131A genes (Figure 1 and HSCs in addition to fibroblasts (26). Entry into at least some of these other cells follows an endocytic, pH-sensitive pathway because of rearrangements among strains. The relative position and orientation of transcripts corresponding to several genes are shown, along with grouping by their putative functional classifications (24, 31, 43–45, 47). This diagram is a simplification, since some and possibly many of the genes shown here have more than one function and other genes that are not shown likely contribute to the indicated processes.

Complementing responses within the infected cell itself are defenses generated by cells of both the innate and the adaptive immune system. Depletion of NK cells in mice results in higher titers of murine CMV in tissues and increased mortality (32). In humans, NK cell deficiency has been linked to severe CMV disease (33). Considerable evidence indicates that adaptive T cell responses are critical for keeping the virus inactive. For example, restoration of CD8+ and CD4+ T cells is a strong correlate of control of the virus after HSC transplant (HSCT; ref. 34). Moreover, adoptive transfer of CMV-specific T cells protects against clinical reactivation (35, 36).

In seropositive humans, a strikingly high fraction (10% or more) of circulating T lymphocytes target CMV (37). Use of tetramers has shown that pp65 is recognized by a high fraction T cells, but many other gene products are also recognized (37, 38). Moreover, the fraction of CMV-specific T cells tends to increase with age, which supports the hypothesis that CMV contributes to immune system exhaustion and dysfunction associated with aging (39).

Antibodies in CMV-infected individuals have been useful for establishing serostatus. Although it has long been thought that only antibodies to gB or gH neutralize the virus, the finding that other viral genes, including UL128, UL130, and UL131A, mediate entry into endothelial and epithelial cells raises new possibilities for therapeutic design. In fact, recent data indicate that neutralizing antibody titers in human sera may be two logs higher against these alternative entry pathway mediators compared with those targeting against gB and gH (40–42). Thus, future studies should revisit the possible role of antibody responses in controlling infections, and these genes will be important to consider in designing future vaccines.

Viral counterattack

Faced with such a breadth of host defense systems, the success of CMV in human infection has necessitated evolution of myriad viral evasion strategies. Proteins delivered with infecting virion (e.g., pp65 [UL83], pp71 [UL82], pTRS1, and pRS1) and made very early after infection (UL36, UL37, IE1, and IE2) block intrinsic cellular defenses, including induction of apoptosis, production of interferon and interferon-stimulated genes, and shut off of protein synthesis (31, 43). CMV also interferes with the cellular immune responses (44, 45). At least seven genes are able to modulate, and in many cases inhibit, NK cell function (Figure 1 and ref. 45). For example, the viral miRNA miR-UL112 acts synergistically with a cellular miRNA to inhibit expression of the NK-activating ligand MICB (46). Several genes clustered in the US2-11 region prevent presentation of CMV peptides to T cells. US3 binds to and sequesters MHC class I in the ER, US6 inhibits loading of peptides onto the MHC complex, and US2 and US11 cause dislocation of class I molecules from the ER to the cytosol, where they are degraded.

CMV encodes chemokines, chemokine receptors, and cytokines that likely participate in immune evasion (Figure 1 and ref. 47). For
example, cmvIL-10, which is only 27% identical to human IL-10 but binds to the same receptor and signals through a similar pathway, appears to be primarily immunosuppressive (48). It inhibits proliferation and cytokine production by peripheral blood mononuclear cells and inhibits maturation and stimulates apoptosis of dendritic cells. However, it also has potentially immunostimulatory effects, such as augmenting phagocytic activity of monocytes. Both cmvIL-10 and the CMV chemokine receptor US28 stimulate migration of some cell types, but inhibit migration of others. Although inhibition of cell migration might help the virus evade the host immune cells, enhanced cell migration might promote dissemination of virus to new sites, as has been shown for murine CMV (49, 50).

A major challenge for future research will be to dissect the bona fide functions of the immune modulators during infection in humans. Most of these genes are not essential for replication in cell culture (51, 52). Some general insights have and will continue to emerge from studies of animal CMVs, but immune evasion strategies differ in significant ways in different systems, even in human CMV’s well-studied close cousin, rhesus CMV (8–10). More sophisticated animal and cell culture models, along with deep sequencing technology applied to the analysis of gene expression and variation in both CMV strains and their hosts, should shed light on the key interactions of the host immune system and its viral targets.

Millions of years of evolution have led CMV to establish an apparently benign relationship with its host, at least most of the time. However, CMV replication is poised in a delicate balance with host immune system controls, and even relatively minor perturbations, such as pregnancy or admission to an intensive care unit (ICU), allow CMV reactivation, often without overt CMV disease (Figure 2 and refs. 53, 54). In this sense, CMV seems to be a sentinel chicken of immune system dysfunction. Moreover, subtle effects of subclinical reactivation or quiescent CMV infection might contribute to chronic immune system dysfunction and predispose to other illnesses, including infections by other microbes (55, 56).

On the other hand, interactions among infectious agents are exceedingly complex (57); in fact, murine CMV infection has been reported to protect mice against subsequent pathogenic bacterial infection (58). Thus, our understanding of the full spectrum of risks and benefits of CMV infection and its interactions with the host immune system is far from complete.

The latency puzzle

Like other herpesviruses, CMV becomes clinically quiescent after the primary infection is brought under control by the host immune response. The virus is generally believed to persist in a state of cellular latency, in which infected cells are not producing any infectious virus, but retain the complete genome and have the potential to start producing virus at a later time (59). However, it remains possible that clinical quiescence is often a state in which CMV is replicating at a very low level, below the threshold of current detection methods. True cellular latency has been quite convincingly established in the case of murine CMV (60) and likely occurs with human CMV; however, as illustrated by the extraordinarily high frequency of shedding of viral DNA by asymptomatic herpes simplex virus–2–infected individuals (61), extrapolating from animal models to the human setting requires caution.

The site — or, more likely, sites — of CMV latency or persistence in the human are not yet clear. The risk of acquiring CMV by transfusion from asymptomatic donors implicates blood as one site. Indeed, many studies of CMV latency have focused on circulating leukocytes, in large part because of their being relatively accessible...
for research, and these studies have revealed latent infection in immature cells of the myeloid lineage (59). However, these results do not rule out other sites of latency. SOT from seropositive to seronegative donors can transmit CMV (62). Although these organs are undoubtedly contaminated with leukocytes, the fact that the virus has a propensity to reactivate within the transplant- ed organ suggests that parenchymal cells may harbor latent virus.

At least in cell culture models of latency, CMV expresses only a small number of genes (59), as is true of latency in other herpesvirus systems. A particularly intriguing one of these is an alter-
vatively spliced, latency-associated form of cmvIL-10 (LAcmvIL-10), which retains some but not all of the activities of cmvIL-10. Interestingly, LAcmvIL-10 inhibits MHC class II recognition of infected cells and might thus assist in avoiding elimination by the immune system (48). Moreover, since LAcmvIL-10 has immuno-
modulatory properties and might be secreted from latently infect-
ed cells for decades, it has the potential to cause chronic immune system dysfunction in otherwise healthy individuals. Clarification of the genes expressed during bona fide latency and elucidating their effects on the host will require much additional research.

**CMV infection and disease**

The common manifestations of CMV infection depend to a large extent on the particular clinical setting. Overt disease is limited primarily to patients with significant immune system dysfunction that can result from other illnesses or iatrogenic causes (Figure 2).

*Congenital and neonatal infection.* CMV is the most frequent con-
genital viral infection, occurring in as many as 40,000 cases in the United States each year. A recent review of multiple studies found that of infected infants, 13% had symptoms at birth, and in 0.5%, the infection proved fatal (63). Approximately 20% of the total — primarily, but not exclusively, those symptomatic at birth — suffer from permanent sequelae, commonly sensorineural hearing loss (64). Seronegative mothers who become infected during pregnan-
ancy have a much higher risk of transmitting the virus and of bearing an affected infant compared with women who are seropositive at conception, but infants of the latter group can also suffer sequelae (65). It now seems likely that at least some cases result from infec-
tion of the pregnant woman with a new virus, rather than from reactivation of a latent virus the women had acquired earlier (66).

Antiviral treatment of congenital CMV disease with ganciclovir or valganciclovir has been shown to be beneficial (67). The develop-
ment of preventative strategies before pregnancy (i.e., immuni-
ization, ref. 68), during pregnancy (i.e., CMV-specific immunoglobu-
lins, ref. 69, and valacyclovir), and after birth (i.e., newborn CMV screening, screening for late-onset hearing loss, ref. 70, and pre-
emptive treatment) are high-priority research areas.

CMV can also be acquired in the neonatal period via breast milk (71). Reported transmission rates from mothers to preterm infants vary widely (6%–60%) as do disease rates (0%–35%), so the burden and determinants of breast milk transmission are not yet clear (71).

*Immunocompetent hosts.* Judging from data showing increasing seroprevalence with age, acquisition of CMV may occur at any time during life (1). In early childhood, CMV can be acquired via saliva in family or day care settings. During adulthood, CMV is transmis-
ted sexually and via saliva (e.g., from children), and occasionally via blood transusions or transplanted organs (11, 72). Primary infec-
tion is typically asymptomatic, but may present clinically as a mono-
mucositis-like illness. Very occasionally, CMV seems to cause pneu-
monia or gastrointestinal disease in immunocompetent hosts (73).

*Hematologic malignancies and HCT.* CMV pneumonia remains one of the most feared infectious complications following HCT. Even with treatment, mortality remains high (74). CMV gastrointestinal disease, which can affect the upper and lower tracts, is presently the most prevalent manifestation of CMV disease in HCT recipi-
ents (74). Retinitis, hepatitis, and encephalitis occur infrequently.

The most important pretransplant risk factor for CMV disease is the serological status of the donor and recipient, with serosoposi-
tive recipients being at highest risk, followed by CMV-seronega-
tive patients receiving stem cells from a CMV-seropositive donor (referred to as D+/R– patients); seronegative recipients of stem cells from seronegative donors have a very low risk of primary infection if CMV-safe blood products are used (75). Other risk factors for CMV infection include the use of high-dose cortico-
steroids, acute and chronic graft-versus-host disease (GVHD), and use of mismatched or unrelated donors (56). Stem cell source and conditioning regimen only minimally affect the risk of CMV infection and disease, with the exception of umbilical cord blood transplantation, which is associated with reactivation and high disease rates in the absence of antiviral prophylaxis (76). Alem-
tuzumab, an anti-CD52 monoclonal antibody that results in pro-
longed CD4+ lymphopenia, may also lead to high reactivation rates in both transplant and nontransplant patients (77). CMV disease is very rare after autologous transplantation, unless CD34+ selected stem cells are used.

Today, the use of preemptive antiviral therapy or prophylaxis is the standard of care in HCT recipients (78). These strategies have reduced the incidence of CMV disease during the first 3 months from approximately 25%–30% to 5% in seropositive recipients; however, late CMV disease may occur and requires continued surve-
illance in high-risk patients (79).

*SOT.* CMV can cause a febrile syndrome with leukopenia and/or transaminitis (CMV syndrome) as well as other end-organ disease. There seems to be a predilection of clinical disease manifestations for the transplanted organ, possibly caused by minor HLA mismatches promoting local CMV reactivation and replication (62). Therefore, the end-organ disease manifestations differ according to the type of organ transplantation.

The highest risk for CMV disease occurs in CMV D+/R– patients. In contrast to HCT recipients, reactivation disease (in the seropositive recipients) is less common in SOT recipients. Antiviral prophylaxis and preemptive therapy strategies are wide-
ly used in SOT recipients and have led to a reduction of CMV disease during the time they are applied (typically for at least 3 months; refs. 80–82). Despite these advances, late CMV disease continues to be a clinical problem in D+/R– patients receiving antiviral prophylaxis (83). In addition to CMV syndrome and end-organ disease, also called direct effects, CMV causes indirect effects including allograft rejection, decreased graft and patient survival, and predisposition to opportunistic infections and per-
haps malignancies (Figure 2 and ref. 55).

*HIV.* CMV disease occurs in HIV–1–infected persons with advanced immunosuppression (CD4+ counts <50 cells/mm³, HIV load >100,000 copies/ml, and/or prior opportunistic infections). Retinitis is the most common clinical manifestation, followed by gastrointestina
l disease and encephalitis. Since the introduction of combination antiretroviral therapy (ART), the incidence of new cases of CMV end-organ disease has declined dramatically, now occurring most commonly in persons who are not receiving ART or who have failed to respond (84).
are reports that CMV may play a role in immunosenescence (89) subjects (92, 93). In addition to i.v. and oral formulations, ganciclovir have been suggested (86–88). Perhaps most intriguing CMV is causative in these diseases and conditions or a bystander is randomized controlled trials in both transplant and HIV-infected (53, 85). Moreover, associations of CMV with inflammatory bowel transplant recipients. High-dose acyclovir or valacyclovir have been of CMV retinitis (94), no randomized trial has been performed in transplant recipients. The nucleoside monophosphate analog cidofovir and the pyro
kinase, acts as a chain terminator during viral DNA replication. Although cidofovir has been shown to be effective in the treatment of CMV retinitis (94), no randomized trial has been performed in transplant recipients. High-dose acyclovir or valacyclovir have been shown to reduce indirect effects of CMV in D+/R– renal transplant recipients (96). Fomivirsen, an injectable antisense antiviral for CMV retinitis, is no longer marketed, because advances in anti-retroviral therapy have reduced the incidence of CMV retinitis in patients with HIV-1 (97). Drug resistance can develop with all available drugs (91). Mutations affecting the viral UL97 kinase or, less often, the viral DNA polymerase can cause ganciclovir resistance. Since foscarnet and cidofovir do not require phosphorylation by UL97, resistance arises only by mutations of the DNA polymerase gene (91). Some DNA polymerase mutations cause resistance to more than one of these agents. Resistance is most frequently seen in D+/R– SOT recipients (probably as a result of prolonged drug exposure and incomplete suppression of CMV); however, it may also occur in other clinical situations when antiviral drug is given for a prolonged period of time at levels that incompletely suppress CMV infection (98). An increase in viral load should trigger molecular testing for mutations that are associated with resistance and empirical switching to another drug. Other disease associations. In recent years, the ease and sensitivity of diagnostic capabilities have revealed the presence of CMV (or its immunologic correlates) in settings not traditionally known to manifest CMV. Numerous studies have shown that CMV reacti
vates in immunocompetent patients admitted to ICUs, and there appears to be an association with prolonged hospital and ICU stay (53, 85). Moreover, associations of CMV with inflammatory bowel disease, new-onset diabetes, and tumors such as glioblastoma multiforme have been suggested (86–88). Perhaps most intriguing are reports that CMV may play a role in immunosenescence (89) and in the pathogenesis of atherosclerosis (90), possibly through actions of its many immunomodulatory genes (Figure 1). Whether CMV is causative in these diseases and conditions or a bystander is presently the subject of intense research.

Treatments

Current therapies. Ganciclovir, foscarnet, and cidofovir are currently available drugs for CMV treatment and prevention (Table 1). Ganciclovir (and its orally available formulation, valganciclovir) is a guanosine analog that, after phosphorylation by the CMV UL97 kinase, acts as a chain terminator during viral DNA replication. The nucleoside monophosphate analog cidofovir and the pyrophosphate analog foscarnet also inhibit viral DNA polymerase activity, but neither requires prior activation by any other viral protein (91). Ganciclovir products have been tested most widely in randomized controlled trials in both transplant and HIV-infected subjects (92, 93). In addition to i.v. and oral formulations, ganciclovir can be given locally to the eye in patients with sight-threat
ening retinitis (94). Systemic ganciclovir’s principal toxicity is neutropenia. Although foscarnet is as effective as ganciclovir, its main side effects are renal toxicity and electrolyte imbalances (95). Although cidofovir has been shown to be effective in the treatment of CMV retinitis (94), no randomized trial has been performed in transplant recipients. High-dose acyclovir or valacyclo
virotherapy treatment; Electrolyte imbalances; nephrotoxicity; seizures; i.v. only; genotoxic

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Investigational

Maribavir | HCT, SOT | Not effective at low doses; phase III trials ongoing | 101, 102 | Prophylaxis; salvage treatment | Full spectrum unknown to date; taste disturbance |
| CMX001f | HCT | Phase II trials ongoing | 99 | Prophylaxis; treatment | Full spectrum unknown to date |
| AIC246 | HCT | Phase II trials ongoing | 100 | Prophylaxis | Full spectrum unknown to date |

fFindings of animal studies. gNo published studies. hNo longer available in the United States. iHigh doses. jHDP cidofovir.
The development of vaccines has been a primary goal for controlling CMV. Indeed, an Institute of Medicine report declared that development of a CMV vaccine should be a top priority (113). After decades of development and incremental advances (114), the recent report that a subunit vaccine, consisting of CMV gB with MF59 adjuvant, reduced acquisition of CMV in seronegative mothers who had recently given birth (68) was a major advance. However, this vaccine reduced CMV acquisition by only 50%, possibly because the vaccine could not induce antibodies that prevent entry into endothelial and epithelial cells (40–42). Other approaches to vaccine development are being studied, including chimeric live-attenuated vaccines, DNA vaccines, and aliphavirus replicons encoding CMV proteins (115). The recent finding that rhesus macaques mount immune responses to antigens delivered by repeated sequential inoculation of rhesus CMV recombinants highlights a potential role for live CMV vaccine vectors, but also illustrates the challenges in developing a vaccine that can block CMV infection itself (116).

Future directions

Decades of CMV research have resulted in remarkable advances in our understanding of basic CMV biology and mechanisms of immunologic control. However, many questions remain about the functions of numerous CMV genes, the mechanism of latency, and the pathogenetic processes that account for differing disease manifestations in various clinical settings. Nonetheless, enormous progress has been made in diagnostics, drug therapy, immunotherapy, and vaccine development. At the same time, it has become apparent that the spectrum of CMV morbidity may be much larger than originally appreciated. One task for the future will be to assess conclusively whether CMV is a pathogen or bystander in critically ill pediatric and adult patients as well as in other diseases such as atherosclerosis, inflammatory bowel disease, and tumors, including glioblastoma multiforme. The possible role of CMV in immunosenescence is particularly interesting and will be a field of active research for years to come. New therapeutics with improved toxicity profiles are urgently needed, not only for transplant recipients, but also for congenital disease and possibly for future new indications in immunocompromised persons. Meanwhile, management strategies with currently available drugs should be optimized. The field of adoptive T cell immunotherapy is also well on its way to overcoming obstacles that have prevented widespread application, including the time needed to generate sufficient numbers of T cells and failure to restore persisting T cell immunity in the presence of high-dose steroids (117). Finally, exciting developments toward a CMV vaccine, arguably the holy grail of prevention, are underway (68). Thus, myriad challenges remain, but judging from recent progress, we suspect that major advances are on the horizon.

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18. Lurain NS, et al. Analysis of the human cytomegalovirus genome region from UL146 through UL147A reveals sequence hypervariability, genotypic stabil-
Corrigendum

The contents of this corrigendum are not available.