VIROLOGICA SINICA, December 2008, 23 (6):438-448
DOI 10.1007/s12250-008-3003-2

CLC number: Q786 Document code: A Article ID: 1674-0769 (2008) 06-0438-11

Pathogenetic Consequences of Cytomegalovirus-Host Co-evolution*

Gerardo Abenes and Fenyong Liu**

(Division of Infectious Diseases, School of Public Health, University of California, Berkeley, CA 94720, USA)

Abstract: Co-evolution has been shown to result in an adaptive reciprocal modification in the respective behaviors of interacting populations over time. In the case of host-parasite co-evolution, the adaptive behavior is most evident from the reciprocal change in fitness of host and parasite-manifested in terms of pathogen survival versus host resistance. Cytomegaloviruses and their hosts represent a pairing of populations that has co-evolved over hundreds of years. This review explores the pathogenetic consequences emerging from the behavioral changes caused by co-evolutionary forces on the virus and its host.

Key words: Cytomegalovirus; Co-evolution; Pathogenesis

Co-evolution is the process of reciprocal, adaptive genetic change in two or more species (127, 140). It can occur between any interacting populations, but it is expected to be particularly important in host-pathogen systems because of the intimate nature of the association and the strong selective pressures that each can exert on the other (140). Cytomegaloviruses (CMV) and their hosts are thought to have co-evolved over hundreds of years (40). Recent data brought to light by studies on CMV pathogenesis provide an interesting glimpse on how the lengthy association between virus and host has shaped many of the viral pathogenetic features.

CYTOMEGALOVIRUS BIOLOGY, EPIDEMIOLOGY AND PATHOGENESIS

Human CMV (HCMV) is a ubiquitous human herpesvirus that infects a great majority of the world's population. The virus is a member of the β-group of herpesviruses characterized by their strict host specificity, comparatively large genome, and slow growth in culture (66, 80). Cells infected with the virus present a characteristic ballooned-cytopathology from which the name of the etiologic agent -"cytomegalovirus"- was derived (117, 118, 138). The linear double stranded viral DNA genome of 200-240 kbp encodes at least 150 proteins, many of which contribute to making the virus one of the most successful intracellular parasites in nature (25, 31, 81, 82, 98, 133).

The worldwide incidence of HCMV infection varies widely from 60%-100% (40, 122). Disparity in the incidence of the disease among population groups is influenced by prevailing health, hygiene, and socio-economic status (40, 86, 102, 122). Although the infection is mostly well tolerated by people with intact

Received: 2008-09-09, Accepted: 2008-09-24

* Foundation items: This work was, in part, supported by US Public Health Service (NIH grants AI041927, AI050468, DE014145, and DE016813).

** Corresponding author.
Tel: +1-510-643-2436, Fax: +1-510-643-9955,
E-mail: liu_fy@uclink4.berkeley.edu

immune systems, it can be life threatening or severely debilitating for immunocompromised individuals such as AIDS patients, cancer patients, organ or tissue transplant recipients undergoing immunosuppressive therapy, infants, fetuses, and the elderly (1, 33, 34, 86, 87, 102, 129).

Like other herpesviruses, the CMV infectious cycle starts with an acute episode which progresses to a persistent stage that paves the way to the latent state (1, 49, 62, 66). Acute infection is usually precipitated by contact of virus with epithelial body surfaces but may also occur after organ transplant, blood transfusion, or as a result of congenital or perinatal infection (17, 24, 88, 104-106). It is characterized by robust viral replication at the site of primary infection and may become disseminated systemically via the lymphatic system then through cell-associated viremia. Terminal cases of acute CMV infection typically reveal widespread lesions of cellular cytomegaly in almost all organs of the body (94). The most common cell types found to be infected at autopsy are ductal epithelial cells, but other cell types also known to be infected are endothelial cells, smooth muscle cells, hepatocytes, granulocytes, monocytes, neurons, and glial cells (61, 65, 66, 93, 113, 129).

The persistent phase of CMV disease is characterized by low-level viral replication in infected organs. There is intermittent viral shedding in body fluids due to persistent infection of ductal epithelia. This stage usually presages latent infection wherein the infected host is negative for virus excretion but harbor the viral genome in a non-replicative form in some cells (49, 50, 99, 111, 112, 114). Latent virus may reactivate when the host is immunosupressed or presumably, when the latently infected progenitor cell undergoes differentiation into the mature phenotype (112, 114, 119, 120). The molecular mechanisms underlying viral reactivation from latency are not well understood. In the blood mononuclear cell lineage where data are most abundant, it has been shown that latently infected monocyte progenitor cells reactivate the virus in the course of terminal differentiation. Interestingly, reactivation appears to be associated with chromatin remodeling that accompanies cellular differentiation. Indeed, in one model, it has been shown that euchromatin formation resulting from acetylation of histone tails also loosens important regions in the latent viral DNA, notably the IE region, thereby allowing access of factors involved in initiating viral transcription that culminate in reactivation (101).

CMV disease is transmitted vertically from mother to offspring, or horizontally between individuals (1, 62, 87, 88). Vertical transmission can occur transplacentally, during birth, or through breast milk (5, 7, 17, 24, 57, 92, 109). Horizontal transmission can occur by direct exchange of body fluids, organ/tissue transplantation, or through contaminated materials as occurs in day care centers (32, 84, 142).

CO-EVOLUTION AND CMV PATHOGENESIS

Reciprocal traits involved in pathogen-host co-evolution usually operate in opposite directions: what enhances fitness of the host diminishes the fitness of the pathogen, and vice-versa (140). In the context of CMV-host co-evolution, enhanced features of the virus include focused resources towards infecting a specific host species, striking evasive adaptability to the host's repertoire of antiviral strategies, and ability to perpetuate itself in the host. As such, CMVs, do not cross the species barrier (54, 108, 125), they have

developed cunning ways of evading the host immune response (9-12, 14-16, 19, 26, 29, 37, 48, 52, 56, 68, 69, 71, 79, 96, 135, 136), they code for functions that temper host perturbation (31) or delay apoptosis of infected cells (41, 42, 77, 115, 126), and most importantly- they can establish latency and subsequently reactivate when the conditions are right (100, 101, 111, 112, 114).

On the part of the virus' co-evolutionary partner- the host, the reciprocal loss of fitness is reflected in terms of pathogenetic manifestations that include prolonged persistence or life-long latent infection with recurrent disease episodes or periodic reactivation, autoimmune syndromes, inflammaging and immunosenescence.

Persistent or Life-long Latent Infection

The hallmark of all herpesvirus infections is prolonged persistence and latent infection. After an initial acute episode in which the virus goes through a burst of robust replication in various organ systems, the virus transitions into a low-level replication stage with intermittent shedding by the infected host. This is the persistent stage of CMV infection and it probably mirrors the shifting events between the host immune system and the viral replication machinery. At the host end, NK cells and other components of the cellular immune system are actively trying to root out infection; on the virus end, gene products are actively trying to subvert the host immune system in order to escape it.

Among the viral gene products reputed to modulate host immune function by interfering with natural killer (NK) cell activity are the gene products of UL40, pUL18, and UL16 of the human virus, and those of m155 and M157 of the mouse virus (MCMV). UL40 gene product upregulates HLA-E expression for recognition by inhibitory NK cell receptors, pUL18 (MHC I heavy chain homologue) replaces host MHC I in infected cell surface and bind natural killer inhibitory receptors (KIRs) (21, 134), UL16 upregulates expression of UL-binding proteins (ULBPs) that sequester NKG2D ligands (22, 30, 124), m155 of MCMV downregulates expression of H60 which is a high affinity ligand for activating receptor NKG2D (70), M157 of MCMV binds to an inhibitory NK receptor in susceptible mice and to an activating receptor (Ly-49H) in resistant mice (4, 116).

The virus also tampers with the host immune function by interfering with MHC I gene expression and antigen processing. For example, US2 and US11 displace the heavy chain from the ER to the cytosol where it is degraded by proteosome (38, 139), US6 binds to TAP and prevents transport of peptides produced in the proteasome to the ER (3, 43, 67), and US3 promotes retention of assembled MHC molecules in the ER (2, 53).

The virus' repertoire for immune modulation also includes chemokine perturbation, exemplified as follows. HCMV encodes chemokine receptor homologues (e.g. US28) that can act as a chemokine sink-sequestering chemokines and preventing them from activating target effectors (97). The UL146 gene product also causes chemotaxis of cells harboring the homologous receptor, thus acting as a bait to propagate infection to other cells (97). UL111.5A, a homologue of IL-10 that functions to dampen host inflammatory response, has been found to be expressed during viral latency in granulocyte-macrophage progenitor cells (51); presumably, protecting infected cells from the influx of inflammatory cells.

One might question whether viral latency actually represents as much a triumph for the virus as it is for the host. It is clear that the host immune system is a factor in maintaining the viral latent state since immunosuppression elicits reactivation. Nevertheless, from the viral perspective, the latent state also allows for a relatively safe refuge in the host and freedom from immunologic threat and elimination. Moreover, the latent state provides the virus the opportunity to wait out a hostile environment and the chance to reactivate as soon as conditions become more favorable.

Autoimmune Syndromes

Because part of the viral armamentarium for survival consists of molecular mimics of host proteins, and because persistent CMV infection and its intermittent reactivation put constant immunological pressure on the host, it has been suggested that CMV infection predisposes the host to develop autoimmune disorders. Indeed, antibodies directed against some viral proteins have been found to cross-react with the host proteins that they resemble. Alternatively, sera from individuals suffering from autoimmune diseases have been shown to react with CMV viral antigens. Examples of autoimmune disorders with known or suspected links to CMV are rheumatoid arthritis (RA) (45, 76, 78, 121), Systemic Lupus Erythematosus (SLE) (27, 46, 110), Inflammatory Bowel Disease (IBD) (23, 28, 44,47, 63, 103), Systemic Sclerosis (Ssc) (72-74, 83, 85), and vascular diseases such as atherosclerosis, restenosis, and transplant vascular stenosis (13, 72, 75, 123, 141).

CMV involvement in RA is thought to be related to production of rheumatoid factors (RFs) in the form of antiidiotypic antibodies to anti-viral Fc gamma-binding proteins (FcBPs) of CMV and other herpesviruses (91, 128). In SLE, a large array of autoantibodies is produced that primarily target the whole chromatin (antinucleosome) and its individual components, dsDNA and histones (64). Apoptotic defects and impaired removal of apoptotic cells could contribute to an overload of autoantigens (and in particular of nucleosomes) in circulation or in target tissues that could become available to initiate an autoimmune response (20, 64, 74). Clinical evidence of CMV involvement in SLE is mounting (20, 46, 110).

The chronic mucosal inflammation in IBD is caused by hyperactivation of effector immune cells, which produce high levels of pro-inflammatory cytokines like tumor necrosis factor-alpha, interleukin-6 and interferon-gamma, resulting in colonic tissue damage (6). The nuclear transcription factor NF-kB was identified as one of the key regulators in this immunological setting. NF-kB activation is markedly induced in IBD patients and it strongly influences the course of mucosal inflammation through its ability to promote the expression of various pro-inflammatory genes. CMV genome is frequently found in IBD tissues, and epidemiologic studies strongly suggest association between the virus and the disease, although a definite causal relationship is yet to be established (23, 28, 95, 131).

Lunardi *et al* showed that in Ssc, endothelial cells undergo apoptosis following tetraspan novel antigen-2 (NAG-2) receptor binding by antibodies directed against the HCMV UL94 protein (73, 83). Moreover, they also showed that anti-HCMV antibodies not only caused endothelial cell activation and apoptosis but also activation of fibroblasts, which is a hallmark of the disease (74). The vascular endothelial injury,

with intimal proliferation and luminal narrowing in arteries and arterioles, excessive extracellular matrix accumulation, and fibroblast activation presumably leads to fibrosis of the skin and internal organs. Namboordiri *et al*. also showed significantly higher antibodies to HCMV UL83 among SSc patients, but could not detect any major Ssc autoantibody related to this protein (83).

In atherosclerosis, apoptosis and cytotoxic damage to endothelial cells have been attributed to binding of receptors and HSP 60 by antibodies directed to US28 and UL122 proteins resulting in plaque-formation and narrowing of involved blood vessel (8, 72, 75). Recently, HCMV infection has also been shown to result in increased endothelial cell proliferation, motility, and capillary tube formation (13). The observed HCMV-induced angiogenic response depended on viral binding to and signaling through the β1 and β3 integrins and the epidermal growth factor receptor, via their ability to activate the phosphatidylinositol 3- kinase and the mitogen-activated protein kinase signaling pathways.

Inflammaging and Immunosenescence

These terms have found their way into scientific literatures fairly recently as a result of growing consciousness for the health and welfare of the rapidly graying segment of the population. Inflammaging has been proposed to describe the low-grade, chronic, systemic inflammatory state that characterizes the aging process (39), while immunosenescence describes the decline in immunologic responsiveness due to adaptive remodeling of parts of the immune system that occurs with age (18, 36, 58). Both conditions are related to chronic antigenic exposure to a variety of antigens, especially to some viruses, and contribute significantly to age-associated morbidity and mortality (35, 90). Presumably, the extended and sustained immunologic burden that occurs with chronic infections causes deterioration of clonotypic immunity, while innate immunity is largely preserved. There is accumulation of memory effector T-cells and exhaustion of naïve T-cells that is further exacerbated by the age-related involution of the thymus (18, 36). Emerging data suggest that CMV is a major contributor in inflammaging and immunosenescence because of its chronicity, widespread incidence, and immunogenicity (55, 107, 132, 137). Lifelong infection with CMV causes chronic antigenic stress resulting in the accumulation of anergic, apoptosis-resistant CD8 T-cells that burden the immune system (60, 89). Indeed, CMV seropositivity among the elderly is associated with oligoclonal expansion of T cells, especially CD8 cells of which as much as 10-14% carry receptors for just a single HCMV epitope (59, 130). Such a specific oligoclonal CD8 expansion, especially in the elderly, squanders limited immunologic space and is regarded to be a poor prognostic factor for survival in the elderly.

CONCLUSION

The co-evolution of CMV with its host has remarkably increased CMV's success in perpetuating itself in nature. As a result of its long-term intimate interaction with the host, CMV has acquired a complex array of functions to counterbalance the defensive repertoire of its host. In keeping with the principle that reciprocal traits involved in pathogen-host co-evolution operate in opposite directions, the enhanced viral fitness is mirrored by the diminished fitness of the host. Consequently, the host is overrun by a wide spectrum of diseases, many of which reflect the virus-host co-evolutionary struggle.

Acknowledgments

We thank Paul Rider for helpful suggestions and comments on the manuscript. This work was, in part, supported by US Public Health Service (NIH grants AI041927, AI050468, DE014145, and DE016813).

References

1. **Adler S P, Marshall B.** 2007. Cytomegalovirus infections. **Pediatr Rev**, 28: 92-100.
2. **Ahn K, Angulo A, Ghazal P, *et al.*** 1996. Human cytomegalovirus inhibits antigen presentation by a sequential multistep process. **Proc Natl Acad Sci USA,** 93: 10990-10995.
3. **Ahn K, Gruhler A, Galocha B, *et al.*** 1997. The ER-luminal domain of the HCMV glycoprotein US6 inhibits peptide translocation by TAP. **Immunity**, 6: 613-621.
4. **Arase H, Mocarski E S, Campbell A E, *et al.*** 2002. Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. **Science,** 296: 1323-1326.
5. **Askin D F.** 2004. Intrauterine infections. **Neonatal Netw**, 23: 23-30.
6. **Atreya I, Atreya R, Neurath M F.** 2008. NF-kappaB in inflammatory bowel disease. **J Intern Med,** 263**:**591-596.
7. **Bale J F.** 2002. Congenital infections. **Neurol Clin**, 20**:** 1039-1060.
8. **Bason C, Corrocher R, Lunardi C, *et al.*** 2003. Interaction of antibodies against cytomegalovirus with heat-shock protein 60 in pathogenesis of atherosclerosis. **Lancet,** 362: 1971-1977.
9. **Basta S, Bennink J R.** 2003. A survival game of hide and seek: cytomegaloviruses and MHC class I antigen presentation pathways. **Viral Immunol,** 16: 231-242.
10. **Bauer D, Tampe R.** 2002. Herpes viral proteins blocking the transporter associated with antigen processing TAP--from genes to function and structure. **Curr Top Microbiol Immunol,** 269: 87-99.
11. **Bego M G, St Jeor S.** 2006. Human cytomegalovirus infection of cells of hematopoietic origin: HCMV-induced immunosuppression, immune evasion, and latency. **Exp Hematol,** 34: 555-570.
12. **Beisser P S, Goh C S, Cohen F E, *et al.*** 2002. Viral chemokine receptors and chemokines in human cytomegalovirus trafficking and interaction with the immune system. CMV chemokine receptors. **Curr Top Microbiol Immunol,** 269: 203-34.
13. **Bentz G L, Yurochko A D.** 2008. Human CMV infection of endothelial cells induces an angiogenic response through viral binding to EGF receptor and beta1 and beta3 integrins. **Proc Natl Acad Sci USA,** 105: 5531-5536.
14. **Boomker J M, de Jong E K, de Leij L F, *et al.*** 2006. Chemokine scavenging by the human cytomegalovirus chemokine decoy receptor US28 does not inhibit monocyte adherence to activated endothelium. **Antiviral Res**, 69: 124-127.
15. **Boomker J M, van Luyn M J, The T H, *et al.*** 2005. US28 actions in HCMV infection: lessons from a versatile hijacker. **Rev Med Virol,** 15: 269-282.
16. **Braud V M, Tomasec P, Wilkinson G W.** 2002. Viral evasion of natural killer cells during human cytomegalovirus infection. **Curr Top Microbiol Immunol,** 269: 117-129.
17. **Bryant P, Morley C, Garland S, *et al.*** 2002. Cytomegalovirus transmission from breast milk in premature babies: does it matter? **Arch Dis Child Fetal Neonatal Ed**, 87: F75-77.
18. **Candore G, Balistreri C R, Colonna-Romano G, *et al.*** 2008. Immunosenescence and anti-immunosenescence therapies: the case of probiotics. **Rejuvenation Res**, 11: 425-432.
19. **Chalupny N J, Rein-Weston A, Dosch S, *et al.*** 2006. Down-regulation of the NKG2D ligand MICA by the human cytomegalovirus glycoprotein UL142. **Biochem Biophys Res Commun,** 346: 175-181.
20. **Chang M, Pan M R, Chen D Y, *et al.*** 2006. Human cytomegalovirus pp65 lower matrix protein: a humoral immunogen for systemic lupus erythematosus patients and autoantibody accelerator for NZB/W F1 mice. **Clin Exp Immunol,** 143: 167-179.
21. **Chapman T L, Heikeman A P, Bjorkman P J.** 1999. The inhibitory receptor LIR-1 uses a common binding interaction to recognize class I MHC molecules and the viral homolog UL18. **Immunity**, 11: 603-613.

22. **Cosman D, Mullberg J, Sutherland C L, *et al.*** 2001. ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the NKG2D receptor. **Immunity**, 14: 123-133.
23. **Criscuoli V, Rizzuto M R, Cottone M.** 2006. Cytomegalovirus and inflammatory bowel disease: is there a link? **World J Gastroenterol,** 12: 4813-4818.
24. **Damato E G, Winnen C W.** 2002. Cytomegalovirus infection: perinatal implications. **J Obstet Gynecol Neonatal Nurs**, 31: 86-92.
25. **Davison A J, Dolan A, Akter P, *et al.*** 2003. The human cytomegalovirus genome revisited: comparison with the chimpanzee cytomegalovirus genome. **J Gen Virol**, 84: 17-28.
26. **DeFilippis V R.** 2007. Induction and evasion of the type I interferon response by cytomegaloviruses. **Adv Exp Med Biol**, 598:309-24.
27. **Diaz F, Urkijo J C, Mendoza F, *et al.*** 2006. Systemic lupus erythematosus associated with acute cytomegalovirus infection. **J Clin Rheumatol**, 12: 263-264.
28. **Dimitroulia E, Spanakis N, Konstantinidou A E, *et al.*** 2006. Frequent detection of cytomegalovirus in the intestine of patients with inflammatory bowel disease. **Inflamm Bowel Dis**, 12: 879-884.
29. **Dugan G E, Hewitt E W.** 2008. Structural and Functional Dissection of the Human Cytomegalovirus Immune Evasion Protein US6. **J Virol,** 82: 3271-3282.
30. **Dunn C, Chalupny N J, Sutherland C L, *et al.*** 2003. Human cytomegalovirus glycoprotein UL16 causes intracellular sequestration of NKG2D ligands, protecting against natural killer cell cytotoxicity. **J Exp Med,** 197: 1427-1439.
31. **Dunn W, Chou C, Li H, *et al.*** 2003. Functional profiling of a human cytomegalovirus genome. **Proc Natl Acad Sci USA**, 100: 14223-14228.
32. **Editorial Comments**. 2004. Cytomegalovirus. **Am J Transplant,** 4 Suppl 10**:** 51-58.
33. **Emery V C.** 2001. Cytomegalovirus and the aging population. **Drugs Aging**, 18: 927-933.
34. **Emery V C.** 2001. Investigation of CMV disease in immunocompromised patients. **J Clin Pathol**, 54: 84-88.
35. **Franceschi C.** 2007. Inflammaging as a major characteristic of old people: can it be prevented or cured? **Nutr Rev**, 65: S173-176.
36. **Franceschi C, Bonafe M.** 2003. Centenarians as a model for healthy aging. Biochem Soc Trans 31: 457-61.
37. **Froberg M K.** 2004. Review: CMV escapes! **Ann Clin Lab Sci**, 34: 123-130.
38. **Gewurz B E, Gaudet R, Tortorella D, *et al.*** 2001. Antigen presentation subverted: Structure of the human cytomegalovirus protein US2 bound to the class I molecule HLA-A2. **Proc Natl Acad Sci USA,** 98: 6794-6799.
39. **Giunta S.** 2006. Is inflammaging an auto[innate] immunity subclinical syndrome? **Immun Ageing**, 3: 12.
40. **Gold E, Nankervis G A.** 1976. Cytomegalovirus. In: **Viral infections of humans: epidemiology and control** (Evans A S ed.), Plenum Press: New York, p 143-161.
41. **Goldmacher V S.** 2005. Cell death suppression by cytomegaloviruses. **Apoptosis,** 10: 251-265.
42. **Goldmacher V S.** 2002. vMIA, a viral inhibitor of apoptosis targeting mitochondria. **Biochimie,** 84: 177-185.
43. **Hengel H, Koopmann J O, Flohr T, *et al.*** 1997. A viral ER-resident glycoprotein inactivates the MHC-encoded peptide transporter. **Immunity**, 6: 623-632.
44. **Hommes D W, Sterringa G, van Deventer S J, *et al.*** 2004. The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. **Inflamm Bowel Dis**, 10: 245-250.
45. **Hooper M, Kallas E G, Coffin D, *et al.*** 1999. Cytomegalovirus seropositivity is associated with the expansion of $CD4^+CD28^-$ and $CD8^+CD28^-$ T cells in rheumatoid arthritis. **J Rheumatol**, 26: 1452-1457.
46. **Hrycek A, Kusmierz D, Mazurek U, *et al.*** 2005. Human cytomegalovirus in patients with systemic lupus erythematosus. **Autoimmunity,** 38: 487-491.
47. **Hussein K, Hayek T, Yassin K, *et al.*** 2006. Acute cytomegalovirus infection associated with the onset of inflammatory bowel disease. **Am J Med Sci,** 331: 40-43.
48. **Jarvis M A, Borton J A, Keech A M, *et al.*** 2006. Human cytomegalovirus attenuates interleukin-1beta and tumor necrosis factor alpha proinflammatory signaling by inhibition of NF-kappaB activation. **J Virol**, 80: 5588- 5598.
49. **Jarvis M A, Nelson J A.** 2002. Human cytomegalovirus

persistence and latency in endothelial cells and macrophages. **Curr Opin Microbiol**, 5**:** 403-407.

50. **Jarvis M A, Nelson J A.** 2002. Mechanisms of human cytomegalovirus persistence and latency. **Front Biosci**, **7:** d1575-1582.
51. **Jenkins C, Abendroth A, Slobedman B.** 2004. A novel viral transcript with homology to human interleukin-10 is expressed during latent human cytomegalovirus infection. **J Virol,** 78: 1440-1447.
52. **Johnson D C, Hegde N R.** 2002. Inhibition of the MHC class II antigen presentation pathway by human cytomegalovirus. **Curr Top Microbiol Immunol**, 269: 101-115.
53. **Jones T R, Wiertz E J, Sun L, *et al.*** 1996. Human cytomegalovirus US3 impairs transport and maturation of major histocompatibility complex class I heavy chains. **Proc Natl Acad Sci USA**, 93: 11327-11333.
54. **Jurak I, Brune W.** 2006. Induction of apoptosis limits cytomegalovirus cross-species infection. **Embo J**, 25: 2634-2642.
55. **Kanapeckiene V, Kalibatas J, Redaitiene E, *et al.*** 2007. The association between cytomegalovirus infection and aging process. **Medicina (Kaunas)**, 43: 419-424.
56. **Kavanagh D G, Hill A B.** 2001. Evasion of cytotoxic T lymphocytes by murine cytomegalovirus. **Semin Immunol,** 13: 19-26.
57. **Kerrey B T, Morrow A, Geraghty S, *et al.*** 2006. Breast milk as a source for acquisition of cytomegalovirus (HCMV) in a premature infant with sepsis syndrome: detection by real-time PCR. **J Clin Virol,** 35: 313-316.
58. **Khan N.** 2007. The immunological burden of human cytomegalovirus infection. **Arch Immunol Ther Exp (Warsz),** 55: 299-308.
59. **Khan N, Hislop A, Gudgeon N, *et al.*** 2004. Herpesvirus-specific CD8 T cell immunity in old age: cytomegalovirus impairs the response to a coresident EBV infection. **J Immunol**, 173: 7481-7489.
60. **Khan N, Shariff N, Cobbold M, *et al.*** 2002. Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. **J Immunol,** 169: 1984-1992.
61. **Khoshnevis M, Tyring S K.** 2002. Cytomegalovirus infections. **Dermatol Clin**, **20:** 291-299, vii.
62. **Kinney J S, Onorato I M, Stewart J A, *et al.*** 1985. Cytomegaloviral infection and disease. **J Infect Dis**, 151: 772-774.
63. **Kojima T, Watanabe T, Hata K, *et al.*** 2006. Cytomegalovirus infection in ulcerative colitis. **Scand J Gastroenterol**, 41: 706-711.
64. **Koutouzov S, Jeronimo A L, Campos H, *et al.*** 2004. Nucleosomes in the pathogenesis of systemic lupus erythematosus. **Rheum Dis Clin North Am**, 30: 529-558, ix.
65. **Krmpotic A, Bubic I, Polic B, *et al.*** 2003. Pathogenesis of murine cytomegalovirus infection. **Microbes Infect**, 5: 1263-1277.
66. **Landolfo S, Gariglio M, Gribaudo G, *et al.*** 2003. The human cytomegalovirus. **Pharmacol Ther,** 98: 269-297.
67. **Lehner P J, Karttunen J T, Wilkinson G W, *et al.*** 1997. The human cytomegalovirus US6 glycoprotein inhibits transporter associated with antigen processing-dependent peptide translocation. **Proc Natl Acad Sci USA,** 94: 6904-6909.
68. **Lenac T, Arapovic J, Traven L, *et al.*** 2008. Murine cytomegalovirus regulation of NKG2D ligands. **Med Microbiol Immunol**, 197: 159-166.
69. **Lin A, Xu H, Yan W.** 2007. Modulation of HLA expression in human cytomegalovirus immune evasion. **Cell Mol Immunol,** 4: 91-98.
70. **Lodoen M B, Abenes G, Umamoto S, *et al.*** 2004. The cytomegalovirus m155 gene product subverts natural killer cell antiviral protection by disruption of H60- NKG2D interactions. **J Exp Med,** 200: 1075-1081.
71. **Loenen W A, Bruggeman C A, Wiertz E J.** 2001. Immune evasion by human cytomegalovirus: lessons in immunology and cell biology. **Semin Immunol,** 13: 41-49.
72. **Lunardi C, Bason C, Corrocher R, *et al.*** 2005. Induction of endothelial cell damage by hCMV molecular mimicry. **Trends Immunol**, 26: 19-24.
73. **Lunardi C, Bason C, Navone R, *et al.*** 2000. Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells. **Nat Med**, 6: 1183-1186.
74. **Lunardi C, Dolcino M, Peterlana D, *et al.*** 2006. Antibodies against human cytomegalovirus in the patho-

genesis of systemic sclerosis: a gene array approach. **PLoS Med,** 3: e2.

75. **Lunardi C, Dolcino M, Peterlana D, *et al.*** 2007. Endothelial cells' activation and apoptosis induced by a subset of antibodies against human cytomegalovirus: relevance to the pathogenesis of atherosclerosis. **PLoS ONE**, 2: e473
76. **Mattey D L, Dawes P T, Nixon N B, *et al.*** 2004. Increased levels of antibodies to cytokeratin 18 in patients with rheumatoid arthritis and ischaemic heart disease. **Ann Rheum Dis**, 63: 420-425.
77. **McCormick A L.** 2008. Control of apoptosis by human cytomegalovirus. **Curr Top Microbiol Immunol**, 325: 281-295.
78. **Mehraein Y, Lennerz C, Ehlhardt S, *et al.*** 2004. Latent Epstein-Barr virus (EBV) infection and cytomegalovirus (CMV) infection in synovial tissue of autoimmune chronic arthritis determined by RNA- and DNA-in situ hybridization. **Mod Pathol,** 17: 781-789.
79. **Mocarski E S.** 2002. Immunomodulation by cytomegaloviruses: manipulative strategies beyond evasion. **Trends Microbiol**, 10**:** 332-339.
80. **Mocarski E S.** Courcelle, C.T. Cytomegalovirus and their replication, In: **Fields' Virology** (Knipe D M, Howley P M, ed.), Lippincott :Philadelphia, p2629-2673.
81. **Murphy E, Rigoutsos I, Shibuya T, *et al.*** 2003. Reevaluation of human cytomegalovirus coding potential. **Proc Natl Acad Sci USA,** 100: 13585-13590.
82. **Murphy E, Yu D, Grimwood J, *et al.*** 2003. Coding potential of laboratory and clinical strains of human cytomegalovirus. **Proc Natl Acad Sci USA,** 100: 14976-14981.
83. **Namboodiri A M, Rocca K M, Kuwana M, *et al.*** 2006. Antibodies to human cytomegalovirus protein UL83 in systemic sclerosis. **Clin Exp Rheumatol,** 24: 176-178.
84. **Noyola D E, Valdez-Lopez B H, Hernandez-Salinas A E, *et al.*** 2005. Cytomegalovirus excretion in children attending day-care centers. **Arch Med Res**, 36: 590-593.
85. **Pandey J P.** 2004. Immunoglobulin GM genes and IgG antibodies to cytomegalovirus in patients with systemic sclerosis. **Clin Exp Rheumatol**, 22: S35-7.
86. **Pass R F.** 2001. Cytomegalovirus, In: **Fields' Virology** (Knipe D M, Howley P M ed.), Lippincott: Philadelphia, p2675-2705.
87. **Pass R F.** 2002. Cytomegalovirus infection. **Pediatr Rev**, 23: 163-170.
88. **Pass R F.** 1985. Epidemiology and transmission of cytomegalovirus. **J Infect Dis**, 152: 243-248.
89. **Pawelec G, Gouttefangeas C.** 2006. T-cell dysregulation caused by chronic antigenic stress: the role of CMV in immunosenescence? **Aging Clin Exp Res**, 18: 171-173.
90. **Pawelec G, Larbi A.** 2008. Immunity and ageing in man: Annual Review 2006/2007. **Exp Gerontol**, 43: 34-38.
91. **Peichl P, Scriba M, Haberhauer G, *et al.*** 1988. Selective binding of rheumatoid factors to antigen structures of cytomegalovirus (CMV). **Scand J Rheumatol**, Suppl 75: 117-122.
92. **Pereira L, Maidji E, McDonagh S, *et al.*** 2005. Insights into viral transmission at the uterine-placental interface. **Trends Microbiol,** 13: 164-174.
93. **Plachter B, Sinzger C, Jahn G.** 1996. Cell types involved in replication and distribution of human cytomegalovirus. **Adv Virus Res,** 46: 195-261.
94. **Rafailidis P I, Mourtzoukou E G, Varbobitis I C, *et al.*** 2008. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. **Virol J**, 5: 47.
95. **Rahbar A, Bostrom L, Soderberg-Naucler C.** 2006. Detection of cytotoxic CD13-specific autoantibodies in sera from patients with ulcerative colitis and Crohn's disease. **J Autoimmun**, 26: 155-164.
96. **Rajagopalan S, Long E O.** 2005. Viral evasion of NK-cell activation. **Trends Immunol,** 26: 403-405.
97. **Randolph-Habecker J R, Rahill B, Torok-Storb B, *et al.*** 2002. The expression of the cytomegalovirus chemokine receptor homolog US28 sequesters biologically active CC chemokines and alters IL-8 production. **Cytokine,** 19: 37-46.
98. **Rawlinson W D, Farrell H E, Barrell B G.** 1996. Analysis of the complete DNA sequence of murine cytomegalovirus. **J Virol**, 70: 8833-8849.
99. **Reddehase M J, Podlech J, Grzimek N K.** 2002. Mouse models of cytomegalovirus latency: overview. **J Clin Virol,** 25 Suppl 2:S23-36.
100. **Reeves M B, Lehner P J, Sissons J G, *et al.*** 2005. An *in vitro* model for the regulation of human cytomegalovirus

latency and reactivation in dendritic cells by chromatin remodelling. **J Gen Virol**, 86: 2949-2954.

101. **Reeves M B, MacAry P A, Lehner P J, *et al.*** 2005. Latency, chromatin remodeling, and reactivation of human cytomegalovirus in the dendritic cells of healthy carriers. **Proc Natl Acad Sci USA,** 102: 4140-4145.
102. **Reynolds D W, Stagno S, Alford C A.** 1981. Chronic congenital and perinatal infections, In: **Neonatal pathophysiolaogy and management in the newborn** (Avery G B, ed.). Lippincott :Philadelphia, p748-789.
103. **Rezania D, Ouban A, Marcet J, *et al.*** 2007. CMV colitis mimicking recurrent inflammatory bowel disease: report of three cases. **Am Surg,** 73: 58-61.
104. **Roback J D.** 2002. CMV and blood transfusions. **Rev Med Virol**, 12: 211-219.
105. **Robinson J.** 2001. Infectious diseases in schools and child care facilities. **Pediatr Rev,** 22: 39-46.
106. **Ross S A, Boppana S B.** 2005. Congenital cytomegalovirus infection: outcome and diagnosis. **Semin Pediatr Infect Dis,** 16: 44-49.
107. **Sansoni P, Vescovini R, Fagnoni F, *et al.*** 2008. The immune system in extreme longevity. **Exp Gerontol,** 43: 61-65.
108. **Scalzo A A, Corbett A J, Rawlinson W D, *et al.*** 2007. The interplay between host and viral factors in shaping the outcome of cytomegalovirus infection. **Immunol Cell Biol**, 85: 46-54.
109. **Schleiss M R.** 2003. Vertically transmitted herpesvirus infections. **Herpes,** 10:4-11.
110. **Sekigawa I, Nawata M, Seta N, *et al.*** 2002. Cytomegalovirus infection in patients with systemic lupus erythematosus. **Clin Exp Rheumatol**, 20: 559-564.
111. **Sinclair J.** 2008. Human cytomegalovirus: Latency and reactivation in the myeloid lineage. **J Clin Virol**, 41: 180-185.
112. **Sinclair J, Sissons P.** 2006. Latency and reactivation of human cytomegalovirus. **J Gen Virol,** 87: 1763-1779.
113. **Sinzger C, Jahn G.** 1996. Human cytomegalovirus cell tropism and pathogenesis. **Intervirology,** 39: 302-319.
114. **Sissons J G, Bain M, Wills M R.** 2002. Latency and reactivation of human cytomegalovirus. **J Infect**, 44: 73-77.
115. **Skaletskaya A, Bartle L M, Chittenden T, *et al.*** 2001. A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation. **Proc Natl Acad Sci USA**, 98: 7829-7834.
116. **Smith H R, Heusel J W, Mehta I K, *et al.*** 2002. Recognition of a virus-encoded ligand by a natural killer cell activation receptor. **Proc Natl Acad Sci USA,** 99: 8826-8831.
117. **Smith M G.** 1956. Propagation in tissue cultures of a cytopathogenic virus from human salivary gland virus (SGV) disease. **Proc Soc Exp Biol Med,** 92: 424-440.
118. **Smith M G.** 1954. Propagation of salivary gland virus of the mouse in tissue cultures. **Proc Soc Exp Biol Med,** 86: 435-440.
119. **Soderberg-Naucler C, Fish K N, Nelson J A.** 1997. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. **Cell,** 91: 119-126.
120. **Soderberg-Naucler C, Streblow D N, Fish K N, *et al.*** 2001. Reactivation of latent human cytomegalovirus in CD14(+) monocytes is differentiation dependent. **J Virol,** 75: 7543-7554.
121. **Stahl H D, Hubner B, Seidl B, *et al.*** 2000. Detection of multiple viral DNA species in synovial tissue and fluid of patients with early arthritis. **Ann Rheum Dis**, 59: 342-346.
122. **Staras S A, Dollard S C, Radford K W, *et al.*** 2006. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. **Clin Infect Dis**, 43: 1143-1151.
123. **Streblow D N, Dumortier J, Moses A V, *et al.*** 2008. Mechanisms of cytomegalovirus-accelerated vascular disease: induction of paracrine factors that promote angiogenesis and wound healing. **Curr Top Microbiol Immunol**, 325: 397-415.
124. **Sutherland C L, Chalupny N J, Schooley K, *et al.*** 2002. UL16-binding proteins, novel MHC class I-related proteins, bind to NKG2D and activate multiple signaling pathways in primary NK cells. **J Immunol,** 168: 671-679.
125. **Tang Q, Maul G G.** 2006. Mouse cytomegalovirus crosses the species barrier with help from a few human cytomegalovirus proteins. **J Virol**, 80: 7510-7521.
126. **Terhune S, Torigoi E, Moorman N, *et al.*** 2007. Human

cytomegalovirus UL38 protein blocks apoptosis. **J Virol,** 81: 3109-3123.

127. **Thompson J N.** 1994. **The Coevolutionary Process**. University of Chicago Press: Chicago, USA.
128. **Tsuchiya N, Murayama T, Yoshinoya S, *et al.*** 1993. Antibodies to human cytomegalovirus 65-kilodalton Fc binding protein in rheumatoid arthritis: idiotypic mimicry hypothesis of rheumatoid factor production. **Autoimmunity**, 15: 39-48.
129. **Vancikova Z, Dvorak P.** 2001. Cytomegalovirus infection in immunocompetent and immunocompromised individuals--a review. **Curr Drug Targets Immune Endocr Metabol Disord**, 1: 179-187.
130. **Vasto S, Colonna-Romano G, Larbi A, *et al.*** 2007. Role of persistent CMV infection in configuring T cell immunity in the elderly. **Immun Ageing,** 4: 2.
131. **Verdonk R C, Haagsma E B, Van Den Berg A P, *et al.*** 2006. Inflammatory bowel disease after liver transplantation: a role for cytomegalovirus infection. **Scand J Gastroenterol,** 41: 205-211.
132. **Vescovini R, Biasini C, Fagnoni F F, *et al.*** 2007. Massive load of functional effector $CD4^+$ and $CD8^+$ T cells against cytomegalovirus in very old subjects. **J Immunol**, 179: 4283-4291.
133. **Vink C, Beuken E, Bruggeman C A.** 2000. Complete DNA sequence of the rat cytomegalovirus genome. **J Virol,** 74: 7656-7665.
134. **Vitale M, Castriconi R, Parolini S, *et al.*** 1999. The leukocyte Ig-like receptor (LIR)-1 for the cytomegalovirus UL18 protein displays a broad specificity for different HLA class I alleles: analysis of LIR-1 + NK cell clones. **Int Immunol,** 11: 29-35.
135. **Voigt S, Mesci A, Ettinger J, *et al.*** 2007. Cytomegalovirus evasion of innate immunity by subversion of the NKR-P1B:Clr-b missing-self axis. **Immunity**, 26: 617- 627.
136. **Wagner C S, Ljunggren H G, Achour A.** 2008. Immune modulation by the human cytomegalovirus-encoded molecule UL18, a mystery yet to be solved. **J Immunol,** 180: 19-24.
137. **Waller E C, Day E, Sissons J G, *et al.*** 2008. Dynamics of T cell memory in human cytomegalovirus infection. **Med Microbiol Immunol,** 197: 83-96.
138. **Weller T H, Hanshaw J B, Scott D E.** 1960. Serological differentiation of viruses responsible for cytomegalic inclusion disease. **Virology,** 12: 130-132.
139. **Wiertz E J, Jones T R, Sun L, *et al.*** 1996. The human cytomegalovirus US11 gene product dislocates MHC class I heavy chains from the endoplasmic reticulum to the cytosol. **Cell**, 84: 769-779.
140. **Woolhouse M E, Webster J P, Domingo E, *et al.*** 2002. Biological and biomedical implications of the co-evolution of pathogens and their hosts. **Nat Genet,** 32: 569-577.
141. **Yi L, Lin J Y, Gao Y, *et al.*** 2008. Detection of human cytomegalovirus in the atherosclerotic cerebral arteries in han population in china. **Acta Virol**, 52: 99-106.
142. **Ziemann M, Krueger S, Maier A B, *et al.*** 2007. High prevalence of cytomegalovirus DNA in plasma samples of blood donors in connection with seroconversion. **Transfusion**, 47: 1972-1983.