Model for MCMV Disease

Subjects: Virology
Contributor: Megan Lloyd

Murine cytomegalovirus (MCMV) is a natural pathogen of mice that is present in all wild mice populations and has been used extensively as an animal model for human cytomegalovirus disease. By manipulating the mouse strain, the type of virus used, the inoculation route and the addition of various chemotherapeutic treatments (e.g. immunosuppression), many human diseases can be modeled in a realistic and consistent way. This entry describes the many ways that MCMV has been used to model human disease.

congenital disease placenta salivary gland

1. Introduction

It has famously been stated that “mice lie and monkeys exaggerate”[1], but the use of animal models in the study of infectious disease provides strong evidence for the mechanisms underlying the pathogenesis of infections in humans and provides opportunities to study interactions between hosts and pathogens that are not provided by collecting minimally invasive human samples such as blood, feces, saliva and urine. When investigating infectious diseases, the ability to correlate tissue histopathology with pathogen replication rates over time or evaluate cell signaling and related immune modulation in the context of a complete immune system is of inestimable value and provides mechanistic information, as well as pre-clinical opportunities to test treatment efficacy and toxicity. The ability of a pathogen to infect both mice and humans allowed the development of Koch’s postulates[2], an evidence framework still used today to prove the association of newly described pathogens with infection and subsequent pathological sequelae, albeit with modifications to account for the presence of pathogens in commensal flora[3] and viruses that are attenuated in a culture[4]. An example of this modern reasoning has been applied for SARS-CoV-1[5].

There are many animal models where laboratory-inoculated animals exhibit symptoms or pathogen replication that mimics human infection, even though infection may not occur in the natural environment. These models are useful in carefully evaluated (and disclosed) circumstances (discussed in[6] for SARS-CoV-2) and have provided useful information on infection pathways and the effects of opportunistic infections and potential drug targets[7]. Examples of animal models in non-target species are those developed for influenza and respiratory syncytial virus in ferrets[8] and Ebola virus infection, which have been modeled in suckling (but not adult) immunocompetent mice as well as Syrian golden hamsters[9]. These models and others like them have illuminated pathways used by pathogens to travel from the site of infection to organs or other sites of tropism, as well as immune responses, symptom and infection profiles and treatment options.

In animal models for viral disease, the presence of the correct receptor used by the virus to enter a cell is critical and needs to be largely conserved between species for cross-species infection to occur[6]. For infections where viruses do not naturally infect another species due to absence of the correct receptor, transgenic mice have been developed that allow an animal model to be developed (e.g., for poliovirus)[10]. Some viruses, such as influenza, naturally infect multiple species (avian species, pigs and humans[11]) while others, such as cytomegalovirus, are species-specific. Animal models where the pathogen naturally infects the animal host and the disease is naturally present in wild populations can provide insights into human disease by illuminating complex host-pathogen interactions and provide clinically relevant data.

Cytomegaloviruses (CMVs) from the family Herpesviridae and the subfamily Betaherpesvirinae are species-specific viruses and have been isolated from many mammalian species (e.g., human, mouse, rat, guinea pig and various primates; see[12] for a discussion). CMVs have evolved with their hosts[13] and generally do not replicate completely in vivo in different species after inoculation, even where in vitro growth has been described (e.g., murine cytomegalovirus (MCMV) will grow in vitro in rat cells but will not grow in vivo in rats[14]). However, there have been reports of the replication of disparate CMV in other species in circumstances where xenotransplantation has taken place and the recipient has received immunosuppressive chemotherapy[15][16]. Juvenile rats have also been reported to support the growth of MCMV, although older rats (>6 weeks old) were not susceptible to infection[17].

2. MCMV as a Model for HCMV Infection

The recorded movement of MCMV between organs differs, depending on the route of infection (described in[33] and [12]). There is a strong tropism for the salivary gland, and active viral replication persists in salivary glands for longer than other organs, regardless of the route of infection used. As with all herpesviruses, MCMV infection has a latent phase[32]. MCMV infection without significant manipulation of the host has successfully been used to model various aspects of human infection (Table 1). Information from this natural animal model has greatly improved the understanding of the pathogenesis of HCMV infection in humans.

Table 1. Human disease caused by human cytomegalovirus (HCMV) modeled by murine cytomegalovirus (MCMV) infection in mice.

Human Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	Effect	Reference
Viremia	Intraperitoneal (i.p) inoculation of BALB/cByJ mice.	SGV/TCV not specified 10^6 PFU	White blood cells have viral DNA but no evidence of *ie1* RNA.	[34]
Viral latency	BALB/c footpad inoculated at 2 weeks of age.	TCV 10^5 PFU	Whole body irradiation leads to reactivation of infection. Antibody protects from viral dissemination.	[35][36]

Human Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	Effect	Reference
	Latency present after 3 weeks.			
Pneumonitis	1. Intranasal inoculation into outbred Swiss mice or intra-tracheal infection of BALB/c mice.	TCV >10^4 PFU	Severe diffuse interstitial pneumonitis closely resembling that seen in immunocompromised patients and in newborn infants, 20% died.	[37]
	2. Inoculation of newborn BALB/c.	SGV, 6 PFU i.p.	Pneumonitis and myocarditis, 95% lethal.	[38]
Hepatitis	i.p inoculation of BALB/c mice.	SGV, 10^5 PFU	Hepatitis evident, dose is Lethal $Dose_{50}$.	[26]
Ocular infection (retinitis)	1. Intraocular inoculation (scarified cornea or through corneal limbus) of IRC/Sic mice. 2. Intraperitoneal inoculation of BALB/c mice.	SGV, Tissue Culture Infectious $Dose_{50}$ values given.	Different effects SGV vs. TCV.	[39]
			Inflammatory response in retina (virus not present) and iris (virus present).	[40]
Excretion of CMV into breastmilk	Acute or latently inoculated C57BL/6 mothers (i.p.), leukocytes from BM positive by *ie1* mRNA detection, RTPCR.	SGV 3×10^2–3×10^4 PFU	Evidence of neonatal infection via breast milk. Inoculation of milk into CD-1 1-day old mice results in infection.	[41]
Arterial blood pressure post CMV infection	i.p. inoculation of 2-week-old C57BL/6 mice.	TCV, 3×10^5 PFU/1mL/mouse	MCMV increased blood pressure independent of diet. Increased serum IL-6, TNF-alpha, and MCP-1.	[42]
Viral myocarditis	i.p. inoculation of C57BL/6 and BALB/c mice.	SGV 10^4 PFU	Inflammatory foci in the heart and infection of cardiac myocytes.	[43]
Infection post bone marrow transplantation	Irradiated BALB/c mice inoculated with virus prior to intravenous (i.v.) purified bone marrow cells.	10^5 PFU	Failure in haematopoiesis, leading to death.	[44]

References

Human Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	Effect	Reference
Sexual transmission of CMV via semen	Spermatozoa plus Smith MCMV artificially inseminated (compared with sperm alone).[47]	SGV 10^5 PFU	Embryos collected on E14. One produced cytopathic effect (second passage). No significant difference with numbers or abnormalities.	[45]

[1] Salivary gland derived virus, [2] Tissue culture-derived virus, [3] Plaque-forming units.

3. Mouse Strain Selection Affects the Severity of MCMV Pathogenesis

Investigations into the effects of MCMV Cairo1 in different mouse strains have been ongoing in the models of different disease states. Initial work focused on LD_{50} calculations (e.g.[46]), and it was found that the H-2 alleles of different mouse strains determined their response to infection, including the production of autoantibodies[47] and the induction of myocarditis[48]. Other mechanisms for resistance to MCMV, such as that demonstrated in C57BL/6 mice compared with BALB/c mice or the differing resistance of New Zealand Black and White mice to MCMV infection, were associated with differences in innate natural killer (NK) cell activation and were strongly associated with particular strains of viruses[49][50]. Where MCMV was used as a vaccine vector expressing the mouse ovarian glycoprotein zona pellucida 3 in studies investigating immune-mediated contraception, the specific m157 (viral ligand) to Ly49H (NK cell activation receptor) rapid response to infection was broadly associated with vaccine success[51]. This effect was abrogated through the use of a different virus strain, G4 (isolated from the salivary glands of a mouse from Geraldton, WA[52]), as the vaccine vector. G4 does not have the same interaction with NK cell activation receptors, and this demonstrates the importance of vector strain selection in the development of recombinant CMV-based vaccines[53].

4. MCMV-Based Models for Human Disease Requiring Chemical, Genetic or Physical Manipulation

A recent systematic review and metanalysis calculated that the worldwide seroprevalence of HCMV is 83%[54]. Increasing CMV disease is broadly associated with improvements in medicine because it is often associated with acute immunosuppression, allowing the reactivation of a latent infection. One of the more serious sequelae of CMV infection is found in solid organ transplant recipients, who often experience reactivation from latency and associated pneumonitis, hepatitis and potential organ rejection (discussed in [55]). The likelihood of severe CMV disease increases when the transplanted organ is from a seropositive donor (previously infected with CMV, with no active viral replication but a strong CMV-specific humoral response) being transplanted into a seronegative recipient[56]. In general, outcomes can be improved with the use of antiviral therapy, with a recent metanalysis suggesting that prophylactic treatment using low doses of valganciclovir provides improved outcomes in kidney transplant recipients [57]. CMV can also cause post-transplantation disease in recipients of allogeneic

4. Prescott, J.; Feldmann, H.; Safronetz, D. Amending Koch's postulates for viral disease: When "growth in pure culture" leads to a loss of virulence. Antivir. Res. 2017, 137, 1–5.
5. Fouchier, R.A.M.; Kuiken, T.; Schutten, M.; van Amerongen, G.; van Doornum, G.J.J.; van den Hoogen, B.G.; Peiris, M.; Lim, W.; Stohr, K.; Osterhaus, A.D.M.E. Koch's postulates fulfilled for SARS virus. Nature 2003, 423, 240.
6. Mallick, J.P.; Simmons, C.P.; Gaudet, J. Animal Models to Study Emerging Technologies Against SARS-CoV-2. Cell Mol. Bioeng. 2020, 13, 293–303.
7. Song, J.; Wang, G.; Hoenerhoff, M.J.; Ruan, J.; Yang, D.; Zhang, J.; Yang, J.; Lester, P.A.; Sigler, R.; Bradley, M.; et al. Bacterial and Pneumocystis Infections in the Lungs of Gene-Knockout Rabbits with Severe Combined Immunodeficiency. Front. Immunol. 2018, 9, 429.
8. Enkirch, T.; von Messling, V. Ferret models of viral pathogenesis. Virology 2015, 479–480, 259–270.
9. St Claire, M.C.; Ragland, D.R.; Bollinger, L.; Jahrling, P.B. Animal Models of Ebolavirus Infection. Comp. Med. 2017, 67, 253–262.
10. Ren, R.; Costantini, F.; Gorgacz, E.J.; Lee, J.J.; Racaniello, V.R. Transgenic mice expressing a human poliovirus receptor: A new model for poliomyelitis. Cell 1990, 63, 353–362.
11. Parrish, C.R.; Holmes, E.C.; Morens, D.M.; Park, E.-C.; Burke, D.S.; Calisher, C.H.; Laughlin, C.A.; Saif, L.J.; Daszak, P. Cross-species virus transmission and the emergence of new epidemic diseases. Microbiol. Mol. Biol. Rev. 2008, 72, 457–470.
12. Shellam, G.R.; Redwood, A.J.; Smith, L.M.; Gorman, S. Cytomegalovirus and other herpesviruses. In The Mouse in Biomedical Research; Fox, J.G., Davisson, M.T., Quimby, F.W., Barthold, S.W., Newcomer, C.E., Smith, A.L., Eds.; Academic Press: San Diego, CA, USA, 2007; pp. 1–48.
13. McGeoch, D.J.; Cook, S.; Dolan, A.; Jamieson, F.E.; Telford, E.A.R. Molecular phylogeny and evolutionary timescale for the family of mammalian herpesviruses. J. Mol. Biol. 1995, 247, 443–458.
14. Sandford, G.R.; Brock, L.E.; Voigt, S.; Forester, C.M.; Burns, W.H. Rat Cytomegalovirus Major Immediate-Early Enhancer Switching Results in Altered Growth Characteristics. J. Virol. 2001, 75,

hematopoietic stem cell transplants, and pre-emptive therapy is often initiated after clinical evidence of CMV reactivation (prior to fulminant disease). The economic burden of this therapy is marked.[58] The mouse model of MCMV has been integral in the prediction of useful therapeutics for these clinical circumstances (reviewed in[59], with a discussion of the appropriate use for this model in reliably predicting human outcomes).

In order to model human diseases concerning cytomegalovirus xenotransplantation as a cause of post-transplantation reactivation, the animal model needs to be manipulated to ensure similarity to human infection. The modification can be due to chemical administration (e.g., corticosteroid use), genetic modification of either the virus or the mouse strain used (e.g., MCMV-deleted m157 virus (Δ157) allows C57BL/6 mice to be used without NK cell activation by the virus) or physiological treatment such as surgery. These modified models are listed in Table 2.

Table 2. Models for Study of Latent Herpes Infections in Laboratory Mouse Strains.

Human Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	C [4]	G [5]	P [6]	Effect	Reference
Reactivation after immunosuppression	i.p. inoculation of C3H/StMice.	SGV subcutaneous infection with 10^4 PFU Latency = 8 months	x			Immunosuppression by rabbit antilymphocyte serum and corticosteroid.	[65]
Pneumonitis	Intranasal MCMV plus cyclophosphamide 24 h after viral inoculation in BALB/c.	SGV 10^5 PFU	x			Interstitial pneumonitis.	[66] Reviewed in [67]
Atherogenesis	MCMV inoculated i.p. in APO-E−/− mice (C57BL/6 J. background).	SGV 10^5 PFU Or 3 × 10^4 PFU TCV	x	x		Larger atherosclerotic lesions in infected mice, potentially caused by upregulation of p38.	[68][69]
Transplant-arteriosclerosis	Human peripheral blood leukocyte/Rag-2−/−γc−/− mouse-xenograft-model inoculated with HCMV.	Segments of mammary artery incubated in vivo with 10^5 PFU HCMV before implantation	x	x		Transplant arteriosclerosis was significantly elevated and increased ICAM-1, PDGF-R-b and macrophages.	[70]
Reactivation of CMV infection post	Immunosuppression of BALB/c mice receiving donor	SGV 10^7 PFU MCMV-Δm157. Mice	x	x		Two-step process: allograft ischemia and reperfusion	[71]

5076–5083.

15. Michaels, M.G.; Jenkins, F.J.; St George, K.; Nalesnik, M.A.; Starzl, T.E.; Rinaldo, C.R. Detection of infectious baboon cytomegalovirus after baboon-to-human liver xenotransplantation. J. Virol. 2001, 75, 2825–2828.
16. Denner, J. Xenotransplantation and porcine cytomegalovirus. Xenotransplantation 2015, 22, 329–335.
17. Smith, C.B.; Wei, L.S.; Griffiths, M. Mouse cytomegalovirus is infectious for rats and alters lymphocyte subsets and spleen cell proliferation. Arch. Virol. 1986, 90, 313–323.
18. Hudson, J.B.; Chantler, J.K.; Loh, L.; Misra, V.; Muller, M.T. Murine Cytomegalovirus—Model for Study of Latent Herpes Infections. Can. J. Public Health 1978, 69, 72.
19. Moro, D.; Lloyd, M.L.; Smith, A.L.; Shellam, G.R.; Lawson, M.A. Murine viruses in an island population of introduced house mice and endemic short-tailed mice in Western Australia. J. Wildl. Dis. 1999, 35, 301–310.
20. Smith, A.L.; Singleton, G.R.; Hansen, G.M.; Shellam, G. A serologic survey for viruses and Mycoplasma pulmonis among wild house mice (Mus domesticus) in southeastern Australia. J. Wildl. Dis. 1993, 29, 219–229.
21. Rawlinson, W.D.; Farrell, H.E.; Barrell, B.G. Analysis of the complete DNA sequence of murine cytomegalovirus. J. Virol. 1996, 70, 8833–8849.
22. Van Damme, E.; Van Loock, M. Functional annotation of human cytomegalovirus gene products: An update. Front. Microbiol. 2014, 5, 218.
23. Wilkinson, G.W.G.; Davison, A.J.; Tomasec, P.; Fielding, C.A.; Aicheler, R.; Murrell, I.; Seirafian, S.; Wang, E.C.Y.; Weekes, M.; Lehner, P.J.; et al. Human cytomegalovirus: Taking the strain. Med. Microbiol. Immun. 2015, 204, 273–284.
24. Cheng, T.P.; Valentine, M.C.; Gault, J.; Pingel, J.T.; Yokoyama, W.M. Stability of Murine Cytomegalovirus Genome after In Vitro and In Vivo Passage. J. Virol. 2010, 84, 2623–2628.
25. Redwood, A.J.; Masters, L.L.; Chan, B.; Leary, S.; Forbes, C.; Jonjić, S.; Juranić Lisnić, V.; Lisnić, B.; Smith, L.M. Repair of an attenuated low passage murine cytomegalovirus bacterial artificial chromosome identifies a novel spliced gene essential for salivary gland tropism. J. Virol. 2020, 94.
26. Brizić, I.; Lisnić, B.; Brune, W.; Hengel, H.; Jonjić, S. Cytomegalovirus Infection: Mouse Model. Curr. Protoc. Immunol. 2018, 122, e51.
27. Osborn, J.E.; Walker, D.L. Virulence and Attenuation of Murine Cytomegalovirus. Infect. Immun. 1971, 3, 228–236.

Human Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	C [4]	G [5]	P [6]	Effect	Reference
organ transplantation	kidney (C57BL/6 allograft) leads to dissemination of reactivated MCMV.	used as donors 4–8 months post i.p. inoculation (latency)				injury (step 1). Immunosuppression mediated viral dissemination (step 2)	
Sjogren's syndrome	1. MCMV inoculated i.p. in *Fas*-deficient C57BL/6 (lpr/lpr) mice. 2. MCMV inoculated i.p. in tumor necrosis factor-α/Kozinowski-inducing ligand deficient BALB/c mice	SGV, 10^5 PFU SGV 10^4 PFU	x	x		Salivary gland inflammation and autoantibody production. Autoantibody production and lymphocytic aggregates.	[72]
Cytomegalovirus disease	1. BALB/c mice undergo sublethal irradiation (6 Gy), undergo syngeneic haematopoietic stem cell transplant 6 h later, 2 h later inoculated with CMV via foot pad. 2. CD8 T cell immunotherapy	TCV 10^3 PFU	x			Pulmonary infection control depends on CD8 T cell reconstitution.	[73]
Reactivation of cytomegalovirus after haemopoietic cell transplantation						Controls CMV associated immunopathology.	[74] Reviewed in [59]
Graft versus host disease	1. Inoculated with MCMV 3 days prior to transplant. A variety of H-2 defined mice inoculated i.v. with spleen cells (either MHC1 or MHCII disparity). 2. Strain specific antibody therapy. Latently inoculated mice (up to 10 weeks)	$1 \times LD_{50}$ SGV	x			Reduction of CTL and immunodeficiency induced, 10 × less donor cells required.	[75]
CMV retinitis	1. Inoculation into supraciliary space (described in [77]) +	10^4 (B6 or B6D2F1) or 5 × 10^3 PFU (BALB/c) SGV 5 × 10^3 PFU	x	x		Strain-specific antibody therapy protects from MCMV reactivation. Retinitis abrogated using i.v. siRNAs directed against	[76] [78][79]

28. Mims, C.A.; Gould, J. Infection of salivary glands, kidneys, adrenals, ovaries and epithelia by murine cytomegalovirus. J. Med. Microbiol. 1978, 12, 113–122.
29. Allan, J.E.; Shellam, G.R. Genetic control of murine cytomegalovirus infection: virus titres in resistant and susceptible strains of mice. Arch. Virol. 1984, 81, 139–150.
30. Grundy, J.E.; Mackenzie, J.S.; Stanley, N.F. Influence of H-2 and non-H-2 genes on resistance to murine cytomegalovirus infection. Infect. Immun. 1981, 32, 277–286.
31. Hudson, J.B.; Misra, V.; Mosmann, T.R. Properties of the multicapsid virions of murine cytomegalovirus. Virology 1976, 72, 224–234.
32. Pollock, J.L.; Virgin, H.W. Latency, without persistence, of murine cytomegalovirus in the spleen and kidney. J. Virol. 1995, 69, 1762–1768.
33. Brune, W.; Hengel, H.; Koszinowski, U.H. A Mouse Model for Cytomegalovirus Infection. Curr. Protoc. Immunol. 2001, 43, 19.7.1–19.7.13.
34. Roback, J.D.; Su, L.; Newman, J.L.; Saakadze, N.; Lezhava, L.J.; Hillyer, C.D. Transfusion-transmitted cytomegalovirus (CMV) infections in a murine model: Characterization of CMV-infected donor mice. Transfusion 2006, 46, 889–895.
35. Reddehase, M.J.; Balthesen, M.; Rapp, M.; Jonjic, S.; Pavic, I.; Koszinowski, U.H. The conditions of primary infection define the load of latent viral genome in organs and the risk of recurrent cytomegalovirus disease. J. Exp. Med. 1994, 179, 185–193.
36. Gonczol, E.; Danczig, E.; Boldogh, I.; Toth, T.; Vaczi, L. In vivo model for the acute, latent and reactivated phases of cytomegalovirus infection. Acta Microbiol. Hung. 1985, 32, 39–47.
37. Jordan, M.C. Interstitial pneumonia and subclinical infection after intranasal inoculation of murine cytomegalivirus. Infect. Immun. 1978, 21, 275–280.
38. Fitzgerald, N.A.; Papadimitriou, J.M.; Shellam, G.R. Cytomegalovirus-induced pneumonitis and myocarditis in newborn mice: A model for perinatal human cytomegalovirus infection. Arch. Virol. 1990, 115, 75–88.
39. Hayashi, K.; Kurihara, I.; Uchida, Y. Studies of Ocular Murine Cytomegalovirus Infection. Investig. Ophthalmol. Vis. Sci. 1985, 26, 486–493.
40. Voigt, V.; Andoniou, C.E.; Schuster, I.S.; Oszmiana, A.; Ong, M.L.; Fleming, P.; Forrester, J.V.; Degli-Esposti, M.A. Cytomegalovirus establishes a latent reservoir and triggers long-lasting inflammation in the eye. PLoS Pathog. 2018, 14, e1007040.
41. Wu, C.A.; Paveglio, S.A.; Lingenheld, E.G.; Zhu, L.; Lefrançois, L.; Puddington, L. Transmission of murine cytomegalovirus in breast milk: A model of natural infection in neonates. J. Virol. 2011, 85, 5115–5124.

Human Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	C [4]	G [5]	P [6]	Effect	Reference
	immunosuppression of BALB/c mice via methylprednisolone every 3 days starting 2 days prior to inoculation.					MCMV immediate early protein-3 (IE-3)	
	immunosuppression using C57Bl/6J intraretinal inoculation PLUS MAIDs	SGV 10^4 PFU	x			(MAIDS = mixture defined in [80]) Severity of effect may be due to suppressor of cytokine signaling (SOCS) 1 and 2.	[81]
Renal allograft loss due to MCMV reactivation (donor positive)	Donor BALB/c recipient C57Bl/6 after renal transplantation.	TCV MCMV or Δm157. Infection with 10^4 PFU (Δm157) all donors. Recipient either 10^4 PFU Δm157/WT or 10^2 Δm157	x	x		Th17 inhibition reduced injury to graft.	[82]
Brain infection in immunosuppressed patients	Severe combined immunodeficient (SCID) mice (BALB/c background), intracranial infection. Virus expressing green fluorescent protein	TCV, 10^6 PFU (GFP) SGV 10^5 PFU wildtype	x	x		Adoptive transfer of MCMV-specific CD4 T cells clears CMV from brain. Treatment prior to infection prevents MCMV replication.	[83]
Hemophagocytic lymphohistiocytosis	IFN-γ-knockout (KO) mice on BALB/c background or BALB/c	SGV, 5 × 10^3 PFU	x			Severity not associated with titer, associated with inflammation.	[84]
Laboratory diagnosis of hepatitis	i.v. inoculation of C57BL/6 mice with marker virus (luciferase, mCherry, SINFEKL)	TCV, 10^6 PFU	x			Blood biochemistry levels given (allowing diagnosis of hepatitis)	[85]

42. Cheng, J.L.; Ke, Q.G.; Jin, Z.; Kocher, G.; Mongan, J.P.; Zhang, J.L.; Crumpacker, C.S. Cytomegalovirus Infection Causes an Increase of Arterial Blood Pressure. PLoS Pathog. 2009, 5, e1000427.
43. Lenzo, J.C.; Fairweather, D.; Cull, V.; Shellam, G.R.; James Lawson, C.M. Characterisation of murine cytomegalovirus myocarditis: Cellular infiltration of the heart and virus persistence. J. Mol. Cell. Cardiol. 2002, 34, 629–640.
44. Mutter, W.; Reddehase, M.J.; Busch, F.W.; Buhring, H.J.; Koszinowski, U.H. Failure in generating hemopoietic stem cells is the primary cause of death from cytomegalovirus disease in the immunocompromised host. J. Exp. Med. 1988, 167, 1645–1658.
45. Young, J.A.; Cheung, K.S.; Lang, D.J. Infection and fertilization of mice after artificial insemination with a mixture of sperm and murine cytomegalovirus. J. Infect. Dis. 1977, 135, 837–840.
46. Chalmer, J.E.; Mackenzie, J.S.; Stanley, N.F. Resistance to murine cytomegalovirus linked to the major histocompatibility complex of the mouse. J. Gen. Virol. 1977, 37, 107–114.
47. Bartholomaeus, W.N.; O'Donoghue, H.; Fox, D.F.; Lawson, C.M.; Shellam, G.R.; Reed, W.D. Multiple autoantibodies following cytomegalovirus infection: Virus distribution and specificity of autoantibodies. Immunology 1988, 64, 397–405.
48. Lawson, C.M.; O'Donoghue, H.L.; Reed, W.D. Mouse cytomegalovirus infection induces antibodies which cross-react with virus and cardiac myosin: A model for the study of molecular mimicry in the pathogenesis of viral myocarditis. Immunology 1992, 75, 513–519.
49. Rodriguez, M.; Sabastian, R.; Clark, P.; Brown, M.G. Cmv1-Independent Antiviral Role of NK Cells Revealed in Murine Cytomegalovirus-Infected New Zealand White Mice. J. Immunol. 2004, 173, 6312–6318.
50. Scalzo, A.A.; Fitzgerald, N.A.; Wallace, C.R.; Gibbons, A.E.; Smart, Y.C.; Burton, R.C.; Shellam, G.R. The effect of the Cmv-1 resistance gene, which is linked to the natural killer cell gene complex, is mediated by natural killer cells. J. Immunol. 1992, 149, 581–589.
51. Lloyd, M.L.; Nikolovski, S.; Lawson, M.A.; Shellam, G.R. Innate antiviral resistance influences the efficacy of a recombinant murine cytomegalovirus immunocontraceptive vaccine. Vaccine 2007, 25, 679–690.
52. Booth, T.W.; Scalzo, A.A.; Carrello, C.; Lyons, P.A.; Farrell, H.E.; Singleton, G.R.; Shellam, G.R. Molecular and biological characterization of new strains of murine cytomegalovirus isolated from wild mice. Arch. Virol. 1993, 132, 209–220.
53. Nikolovski, S.; Lloyd, M.L.; Harvey, N.; Hardy, C.M.; Shellam, G.R.; Redwood, A.J. Overcoming innate host resistance to vaccination: Employing a genetically distinct strain of murine cytomegalovirus avoids vector-mediated resistance to virally vectored immunocontraception. Vaccine 2009, 27, 5226–5232.

5. MCMV Exacerbates the Effects of Other Clinical Diseases

For some models, the addition of MCMV can exacerbate disease, reflecting human disease particularly in the intensive care unit setting. These are generally diseases with an immune modulation component. These models are listed in Table 3.

Table 3. Models demonstrating MCMV-associated effects on other diseases.

Medical Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	Effect	Reference
Ulcerative colitis in CMV-inoculated individuals	T cell receptor alpha−/− mice (C57BL/6 background) inoculated i.p. at 7 days of age with MCMV or MCMV-enhanced GFP	TCV, 5 × 10^5 PFU of MCMV for C57BL/6 mice and 2 × 10^4 PFU of MCMV-EGFP for TCR-alpha−/−	Ulcerative colitis is exacerbated in latently infected mice	[86]
Growth of glioblastoma	Mice inoculated i.p. day 2 or life (P2), tumor injection week 15	TCV 10^3 PFU MCMV-Δm157	Tumor growth and reduction in survival	[87]
CMV reactivation after physical damage	Caecal ligation and puncture in latently i.p. inoculated BALB/c mice	TCV 2 × 10^4 cgrmPFU	Plus *S. aureus* to induce bacterial pneumonia	[88][89]
MCMV infection after cholestasis	C57BL/8 mice bile duct ligated, inoculated i.p. Δm157-MCMV-luciferase	SGV/TCV not specified. 2 × 10^5 PFU	Impaired inflammatory response, but no increase in liver pathology	[90]

54. Zuhair, M.; Smit, G.S.A.; Wallis, G.; Jabbar, F.; Smith, C.; Devleesschauwer, B.; Griffiths, P. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. Rev. Med. Virol. 2019, 29, e2034.
55. Razonable, R.R.; Humar, A. Cytomegalovirus in solid organ transplant recipients—Guidances of the American Society of Transplantation Infectious Diseases Community of Practice. Clin. Transplant. 2019, 33, e13512.
56. Limaye, A.P.; Green, M.L.; Edmison, B.C.; Stevens-Ayers, T.; Chatterton-Kirchmeier, S.; Geballe, A.P.; Singh, N.; Boeckh, M. Prospective Assessment of Cytomegalovirus Immunity in High-Risk Donor Seropositive/Recipient Seronegative Liver Transplant Recipients Receiving Either Preemptive Therapy or Antiviral Prophylaxis. J. Infect. Dis. 2019, 220, 752–760.
57. Hwang, S.D.; Lee, J.H.; Lee, S.W.; Kim, J.K.; Kim, M.J.; Song, J.H. Effect of Low-Dose vs Standard-Dose Valganciclovir in the Prevention of Cytomegalovirus Disease in Kidney Transplantation Recipients: A Systemic Review and Meta-Analysis. Transplant. Proc. 2018, 50, 2473–2478.
58. El Haddad, L.; Ghantoji, S.S.; Park, A.K.; Batista, M.V.; Schelfhout, J.; Hachem, J.; Lobo, Y.; Jiang, Y.; Rondon, G.; Champlin, R.; et al. Clinical and economic burden of pre-emptive therapy of cytomegalovirus infection in hospitalized allogeneic hematopoietic cell transplant recipients. J. Med. Virol. 2020, 92, 86–95.
59. Reddehase, M.J.; Lemmermann, N.A.W. Mouse Model of Cytomegalovirus Disease and Immunotherapy in the Immunocompromised Host: Predictions for Medical Translation that Survived the “Test of Time”. Viruses 2018, 10, 693.
60. Hsu, K.M.; Pratt, J.R.; Akers, W.J.; Achilefu, S.I.; Yokoyama, W.M. Murine cytomegalovirus displays selective infection of cells within hours after systemic administration. J. Gen. Virol. 2009, 90, 33–43.
61. Farrell, H.E.; Davis-Poynter, N.; Bruce, K.; Lawler, C.; Dolken, L.; Mach, M.; Stevenson, P.G. Lymph Node Macrophages Restrict Murine Cytomegalovirus Dissemination. J. Virol. 2015, 89, 7147–7158.
62. Oduro, J.D.; Redeker, A.; Lemmermann, N.A.W.; Ebermann, L.; Marandu, T.F.; Dekhtiarenko, I.; Holzki, J.K.; Busch, D.H.; Arens, R.; Čičin-Sain, L. Murine cytomegalovirus (CMV) infection via the intranasal route offers a robust model of immunity upon mucosal CMV infection. J. Gen. Virol. 2016, 97, 185–195.
63. Farrell, H.E.; Lawler, C.; Tan, C.S.; MacDonald, K.; Bruce, K.; Mach, M.; Davis-Poynter, N.; Stevenson, P.G. Murine Cytomegalovirus Exploits Olfaction To Enter New Hosts. MBio 2016, 7, e00251-16.

Medical Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	Effect	Reference
Melanomas growth, repeated injection recapitulates transient response	Intra-tumoral inoculation of MCMV or ΔgL MCMV (spread deficient) impairs melanoma growth in BALB/c mice	TCV (described in [91]), 5 × 10^5 PFU	Infection of macrophages leads to proinflammatory M1 state	[92]
Idiopathic pulmonary fibrosis	Latent MCMV infection in BALB/c mice (i.p.—4 weeks prior), intratracheal bleomycin	SGV, 10^4 PFU	MCMV-exacerbated fibrosis, activation of TGF-β1	[93]
Experimental autoimmune encephalomyelitis (EAE)	C57BL/6J and CD90/86−/− mice inoculated with MCMV i.p. and 8 days later, EAE induced	SGV, 5 × 10^4 PFU	More severe disease (e.g., enhanced demyelination) severity associated with number of splenic $CD4^+CD28^{null}$ T cells	[94]
Use of bronchiolar lavage (BAL) to detect reactivation of CMV in sepsis	BALB/c mice inoculated with MCMV, sepsis by caecal ligation and puncture	SGV/TCV not specified: 10^2–10^6	PCR of BAL cell pellets similar to that of lung tissue	[95]
Acute colitis	C57BL/6 mice	TCV, 3 × 10^4 PFU	Acceleration of colitis development, but no difference in histology	[96]

64. McWhorter, A.R.; Smith, L.M.; Masters, L.L.; Chan, B.; Shellam, G.R.; Redwood, A.J. Natural Killer Cell Dependent Within-Host Competition Arises during Multiple MCMV Infection: Consequences for Viral Transmission and Evolution. PLoS Pathog. 2013, 9, e1003111.
65. Jordan, M.C.; Shanley, J.D.; Stevens, J.G. Immunosuppression reactivates and disseminates latent murine cytomegalovirus. J. Gen. Virol. 1977, 37, 419–423.
66. Shanley, J.D.; Pesanti, E.L. The relation of viral replication to interstitial pneumonitis in murine cytomegalovirus lung infection. J. Infect. Dis. 1985, 151, 454–458.
67. Fonseca Brito, L.; Brune, W.; Stahl, F.R. Cytomegalovirus (CMV) Pneumonitis: Cell Tropism, Inflammation, and Immunity. Int. J. Mol. Sci. 2019, 20, 3865.
68. Tang-Feldman, Y.J.; Lochhead, S.R.; Lochhead, G.R.; Yu, C.; George, M.; Villablanca, A.C.; Pomeroy, C. Murine cytomegalovirus (MCMV) infection upregulates P38 MAP kinase in aortas of Apo E KO mice: A molecular mechanism for MCMV-induced acceleration of atherosclerosis. J. Cardiovasc. Transl. Res. 2013, 6, 54–64.
69. Hsich, E.; Zhou, Y.F.; Paigen, B.; Johnson, T.M.; Burnett, M.S.; Epstein, S.E. Cytomegalovirus infection increases development of atherosclerosis in Apolipoprotein-E knockout mice. Atherosclerosis 2001, 156, 23–28.
70. Abele-Ohl, S.; Leis, M.; Wollin, M.; Mahmoudian, S.; Hoffmann, J.; Muller, R.; Heim, C.; Spriewald, B.M.; Weyand, M.; Stamminger, T.; et al. Human Cytomegalovirus Infection Leads to Elevated Levels of Transplant Arteriosclerosis in a Humanized Mouse Aortic Xenograft Model. Am. J. Transplant. 2012, 12, 1720–1729.
71. Zhang, Z.; Qiu, L.; Yan, S.; Wang, J.J.; Thomas, P.M.; Kandpal, M.; Zhao, L.; Iovane, A.; Liu, X.F.; Thorp, E.B.; et al. A clinically relevant murine model unmasks a "two-hit" mechanism for reactivation and dissemination of cytomegalovirus after kidney transplant. Am. J. Transplant. 2019, 19, 2421–2433.
72. Fleck, M.; Kern, E.R.; Zhou, T.; Lang, B.; Mountz, J.D. Murine cytomegalovirus induces a Sjögren's syndrome-like disease in C57Bl/6-lpr/lpr mice. Arthritis Rheum. 1998, 41, 2175–2184.
73. Podlech, J.; Holtappels, R.; Pahl-Seibert, M.F.; Steffens, H.P.; Reddehase, M.J. Murine model of interstitial cytomegalovirus pneumonia in syngeneic bone marrow transplantation: Persistence of protective pulmonary CD8-T-cell infiltrates after clearance of acute infection. J. Virol. 2000, 74, 7496–7507.
74. Holtappels, R.; Böhm, V.; Podlech, J.; Reddehase, M.J. CD8 T-cell-based immunotherapy of cytomegalovirus infection: "proof of concept" provided by the murine model. Med. Microbiol. Immun. 2008, 197, 125–134.
75. Via, C.S.; Shanley, J.D.; Shearer, G.M. Synergistic effect of murine cytomegalovirus on the induction of acute graft-vs-host disease involving MHC class I differences only. Analysis of in vitro

Medical Condition	Lab Conditions	SGV [1]/TCV [2] PFU [3]	Effect	Reference
Allergic airway disease	C57BL/6 mice inoculated intra tracheally	TCV, 10^4 PFU	Exposed to ovalbumin, CMV-exacerbated disease	[97]

[1] Salivary gland-derived virus. [2] Tissue culture-derived virus. [3] Plaque-forming units.

76. Martins, J.P.; Andoniou, C.E.; Fleming, P.; Kuns, R.D.; Schuster, I.S.; Voigt, V.; Daly, S.; Varelias, A.; Tey, S.K.; Degli-Esposti, M.A.; et al. Strain-specific antibody therapy prevents cytomegalovirus reactivation after transplantation. Science 2019, 363, 288–293.
77. Zhang, M.; Atherton, S.S. Apoptosis in the retina during MCMV retinitis in immuno suppressed BALB/c mice. J. Clin. Virol. 2002, 25, S137–S147.
78. Mo, J.; Atherton, S.S.; Wang, L.; Liu, S. Autophagy protects against retinal cell death in mouse model of cytomegalovirus retinitis. BMC Ophthalmol. 2019, 19, 146.
79. Marshall, B.; Mo, J.; Covar, J.; Atherton, S.S.; Zhang, M. Decrease of murine cytomegalovirus-induced retinitis by intravenous delivery of immediate early protein-3-specific siRNA. Investig. Ophthalmol. Vis. Sci. 2014, 55, 4151–4157.
80. Dix, R.D.; Cray, C.; Cousins, S.W. Mice immunosuppressed by murine retrovirus infection (MAIDS) are susceptible to cytomegalovirus retinitis. Curr. Eye Res. 1994, 13, 587–595.
81. Alston, C.I.; Dix, R.D. Reduced frequency of murine cytomegalovirus retinitis in C57BL/6 mice correlates with low levels of suppressor of cytokine signaling (SOCS)1 and SOCS3 expression within the eye during corticosteroid-induced immunosuppression. Cytokine 2017, 97, 38–41.
82. Li, M.; Boddeda, S.R.; Chen, B.; Zeng, Q.; Schoeb, T.R.; Velazquez, V.M.; Shimamura, M. NK cell and Th17 responses are differentially induced in murine cytomegalovirus infected renal allografts and vary according to recipient virus dose and strain. Am. J. Transplant. 2018, 18, 2647–2662.
83. Reuter, J.D.; Wilson, J.H.; Idoko, K.E.; van den Pol, A.N. CD4(+) T-cell reconstitution reduces cytomegalovirus in the immunocompromised brain. J. Virol. 2005, 79, 9527–9539.
84. Brisse, E.; Imbrechts, M.; Mitera, T.; Vandenhaute, J.; Wouters, C.H.; Snoeck, R.; Andrei, G.; Matthys, P. Lytic viral replication and immunopathology in a cytomegalovirus-induced mouse model of secondary hemophagocytic lymphohistiocytosis. Virol. J. 2017, 14, 240.
85. Stahl, F.R.; Jung, R.; Jazbutyte, V.; Ostermann, E.; Tödter, S.; Brixel, R.; Kemmer, A.; Halle, S.; Rose-John, S.; Messerle, M.; et al. Laboratory diagnostics of murine blood for detection of mouse cytomegalovirus (MCMV)-induced hepatitis. Sci. Rep. 2018, 8, 14823.
86. Matsumura, K.; Nakase, H.; Kosugi, I.; Honzawa, Y.; Yoshino, T.; Matsuura, M.; Kawasaki, H.; Arai, Y.; Iwashita, T.; Nagasawa, T.; et al. Establishment of a Novel Mouse Model of Ulcerative Colitis with Concomitant Cytomegalovirus Infection: In Vivo Identification of Cytomegalovirus Persistent Infected Cells. Inflamm. Bowel Dis. 2013, 19, 1951–1963.
87. Krenzlin, H.; Behera, P.; Lorenz, V.; Passaro, C.; Zdioruk, M.; Nowicki, M.O.; Grauwet, K.; Zhang, H.; Skubal, M.; Ito, H.; et al. Cytomegalovirus promotes murine glioblastoma growth via pericyte recruitment and angiogenesis. J. Clin. Investig. 2019, 129, 1671–1683.

88. Cook, C.H.; Zhang, Y.; McGuinness, B.J.; Lahm, M.C.; Sedmak, D.D.; Ferguson, R.M. Intra-abdominal bacterial infection reactivates latent pulmonary cytomegalovirus in immunocompetent mice. J. Infect. Dis. 2002, 185, 1395–1400.
89. Hraiech, S.; Bordes, J.; Mège, J.L.; de Lamballerie, X.; Charrel, R.; Bechah, Y.; Pastorino, B.; Guervilly, C.; Forel, J.M.; Adda, M.; et al. Cytomegalovirus reactivation enhances the virulence of Staphylococcus aureus pneumonia in a mouse model. Clin. Microbiol. Infect. 2017, 23, 38–45.
90. Rattay, S.; Graf, D.; Kislat, A.; Homey, B.; Herebian, D.; Häussinger, D.; Hengel, H.; Zimmermann, A.; Schupp, A.K. Anti-inflammatory consequences of bile acid accumulation in virus-infected bile duct ligated mice. PLoS ONE 2018, 13, e0199863.
91. Zurbach, K.A.; Moghbeli, T.; Snyder, C.M. Resolving the titer of murine cytomegalovirus by plaque assay using the M2-10B4 cell line and a low viscosity overlay. Virol. J. 2014, 11, 71.
92. Wilski, N.A.; Del Casale, C.; Purwin, T.J.; Aplin, A.E.; Snyder, C.M. Murine Cytomegalovirus Infection of Melanoma Lesions Delays Tumor Growth by Recruiting and Repolarizing Monocytic Phagocytes in the Tumor. J. Virol. 2019, 93, e00533-19.
93. Li, Y.; Gao, J.; Wang, G.; Fei, G. Latent cytomegalovirus infection exacerbates experimental pulmonary fibrosis by activating TGF-β1. Mol. Med. Rep. 2016, 14, 1297–1301.
94. Vanheusden, M.; Broux, B.; Welten, S.P.M.; Peeters, L.M.; Panagioti, E.; Van Wijmeersch, B.; Somers, V.; Stinissen, P.; Arens, R.; Hellings, N. Cytomegalovirus infection exacerbates autoimmune mediated neuroinflammation. Sci. Rep. 2017, 7, 663.
95. Mansfield, S.; Dwivedi, V.; Byrd, S.; Trgovcich, J.; Griessl, M.; Gutknecht, M.; Cook, C.H. Broncholaveolar lavage to detect cytomegalovirus infection, latency, and reactivation in immune competent hosts. J. Med. Virol. 2016, 88, 1408–1416.
96. Brunson, J.L.; Becker, F.; Stokes, K.Y. The impact of primary and persistent cytomegalovirus infection on the progression of acute colitis in a murine model. Pathophysiology 2015, 22, 31–37.
97. Reuter, S.; Lemmermann, N.A.W.; Maxeiner, J.; Podlech, J.; Beckert, H.; Freitag, K.; Teschner, D.; Ries, F.; Taube, C.; Buhl, R.; et al. Coincident airway exposure to low-potency allergen and cytomegalovirus sensitizes for allergic airway disease by viral activation of migratory dendritic cells. PLoS Pathog. 2019, 15, e1007595.

Retrieved from https://encyclopedia.pub/entry/history/show/16531