Immune Network
http://dx.doi.org/10.4110/in.2015.15.4.186
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

Cytomegalovirus Infection and Memory T Cell Inflation

Jihye Kim, A-Reum Kim and Eui-Cheol Shin*

Laboratory of Immunology and Infectious Diseases, Graduate School of Medical Science and Engineering, KAIST, Daejeon 34141, Korea

Cytomegalovirus (CMV) infection in healthy individuals is usually asymptomatic and results in latent infection. CMV reactivation occasionally occurs in healthy individuals according to their immune status over time. T cell responses to CMV are restricted to a limited number of immunodominant epitopes, as compared to responses to other chronic or persistent viruses. This response results in progressive, prolonged expansion of CMV-specific $CD8^+$ T cells, termed 'memory inflation'. The expanded CMV-specific $CD8^+$ T cell population is extraordinarily large and is more prominent in the elderly. CMV-specific $CD8^+$ T cells possess rather similar phenotypic and functional features to those of replicative senescent T cells. In this review, we discuss the general features of CMV-specific inflationary memory T cells and the factors involved in memory inflation.

[Immune Network 2015;15(4):186-190]

Keywords: Cytomegalovirus, T cells, Senescent T cells, Memory inflation, Immunosenescence

INTRODUCTION

During viral infection, T cells recognize viral epitopes and undergo proliferative expansion. Following elimination of virus, the virus-specific T cell population progressively contracts, and a small population of memory T cells is preserved. However, after infection with cytomegalovirus (CMV), a ubiquitous β-herpesvirus, the virus-specific $CD8^+$ T cell population is maintained, and it accumulates at a high frequency, acquiring a phenotype of effector memory cells (1-4). Although primary CMV infection is usually asymptomatic in healthy individuals, its resolution does not result in complete elimination of the virus from the host. Instead, CMV persists latently in the host, and the latent virus is reactivated according to the immune status of the host (5). Consequently, the CMV-specific $CD8^+$ T cell population is boosted by repeated reactivation of CMV over a lifetime, and its size becomes extraordinarily large, often reaching 20% of total $CD8^+$ T cells (6-8). Most of these T cells are functional, and their populations are maintained throughout the life of the host. This phenomenon of gradual increase in CMV-specific $CD8^+$ T cell population over time is known as memory inflation (1,2,9,10). Although inflationary $CD4^+$ T cells have also been observed, their responses are less exaggerated (11). This peculiar nature of the CMV-specific $CD8^+$ T cell population in the elderly has been considered to be related to senescence in the T cell population. Here, we review the general features of CMV-specific memory T cell inflation. In particular, we focus on the factors that contribute to memory T cell inflation in CMV infection and its potential adverse effects in the elderly.

CHARACTERISTICS OF INFLATIONARY MEMORY T CELLS

Inflationary memory $CD8^+$ T cells are characterized by an

Received on July 2, 2015. Revised on August 8, 2015. Accepted on August 10, 2015.

*Corresponding Author. Eui-Cheol Shin, Laboratory of Immunology and Infectious Diseases, Graduate School of Medical Science and Engineering, KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon, Korea. Tel: 82-42-350-4236; Fax: 82-42-350-4240; E-mail: ecshin@kaist.ac.kr

Abbreviations: MCMV, murine CMV; HCMV, human CMV; CD62L, CD62 L-selectin; IRP, immune risk phenotype

effector memory phenotype in mice, humans, and other primates, whereas non-inflationary memory T cells have a typical phenotype of central memory during the latent phase of the infection (1-4). Inflationary memory $CD8^+$ T cells generally express low levels of lymph node homing markers, such as CD62L and CCR7, and accumulate in non-lymphoid peripheral organs. They also display reduced expression of co-stimulatory receptors such as CD28 and CD27 (1,3), and express large amounts of inhibitory receptors such as KLRG-1 and CD85j in mice and humans, respectively (10,12), but they do not express PD-1 (3,13). Despite the chronic latent nature of CMV infection, inflationary $CD8^+$ T cells are proliferative and are capable of producing effector cytokines such as IFN-γ and TNF-α, and maintain cytotoxicity. These functional features are contrary to those of the exhausted T cells observed in other chronic persistent viral infections (3,14). Although inflationary memory T cells possess a terminally differentiated phenotype, they can constantly turnover and respond to viral reactivation (15).

There was an issue of whether inflationary CMV-specific $CD8^+$ T cells are a polyclonal or an oligoclonal population with restricted T cell receptor (TCR) usage. MHC class I tetramer-positive populations using Vβ8.1 or Vβ 8.2 TCR chain increased in latent murine CMV (MCMV) infection (10). Similarly, in humans, CMV-specific $CD8^+$ T cells are restricted in TCR diversity (16). In this regard, it is considered that T cells with high affinity for CMV epitopes are preferentially selected during acute infection, and they continuously retain their clonal dominance (17).

FACTORS INVOLVED IN MEMORY T CELL INFLATION

Repetitive antigen exposure

One of the main causative factors that originated the notion of memory T cell inflation is the presence of repetitive antigen exposure, which was primarily investigated using murine models (18,19). It was demonstrated that MCMV-driven T cells that were transferred to naïve mice failed to divide, suggesting the requirement of antigen stimulation for memory inflation (3). Inflationary T cells are short-lived, with a half-life of approximately 40～50 days, and exhibit a slow turnover rate through antigen exposure. Cells that are primed early in infection may proliferate and maintain the inflationary T cell population. However, it was reported that naïve precursor cells could also be primed when adoptively transferred to latently infected mice and recruited to the inflationary T cell pool (3). Overall, it is concluded that both naïve precursor cells and memory cells may contribute to the inflating memory cell population over time. Recently, a study showed that low dose infection of MCMV severely hampered the accumulation of inflationary memory T cells, suggesting that the dose of viral inoculum influences the magnitude of memory inflation (20).

Antigen presentation

For memory inflation, the manner of antigen processing and presentation might be also important. CMV is well known for its ability to evade $CD8^+$ T cell responses by interfering with antigen processing and presentation of MHC class I pathways in the infected cells. However, robust $CD8^+$ T cell responses are observed in CMV-infected hosts (21-23). This suggests that CMV-specific $CD8^+$ T cells are primed by cross-presentation of CMV antigens by non-infected professional antigen-presenting cells (24). Interestingly, it was observed that the inflationary response was triggered through antigen presentation by non-hematopoietic cells in lymph nodes at a latent stage of MCMV infection (25). Following expansion in lymph nodes, $CD8^+$ T cells move to non-lymphoid peripheral tissues, where they undergo terminal differentiation and accumulate. However, it was recently reported that inflationary T cell populations are primarily generated by exposure to antigens in blood circulation, suggesting a novel mechanism of MCMV-driven memory inflation (15).

Co-stimulation and cytokines

In addition to TCR stimulation, co-stimulatory molecules and inflammatory cytokines are profoundly involved in effector and memory $CD8^+$ T cell responses (26). The main co-stimulatory receptor for T cells is CD28. However, terminally differentiated $CD8^+$ T cells lose their ability to express CD28. As a result, CD28 does not participate as a T cell co-stimulatory receptor during chronic latent infection (27). Instead, other co-stimulatory receptors such as 4-1BB and OX40 are expressed on T cells after antigen-driven T cell activation, and they contribute to MCMV-specific T cell inflation (28,29). Furthermore, use of a bone marrow chimeric mouse model demonstrates that the CMV-specific inflationary T cell response depends on IL-2. In addition, secondary expansion is engendered by

$CD8^+$ T cell-derived autocrine IL-2 but not by $CD4^+$ T cell- or dendritic cell-generated IL-2 (30,31). IL-7 and IL-15, which are important cytokines for homeostatic proliferation of memory $CD8^+$ T cells, may affect the proliferation of HCMV-specific T cells (32), but their pivotal role in memory T cell inflation remains to be elucidated. IL-10 was shown to clearly inhibit the inflation of T cells in the chronic phase of MCMV infection, but the specific molecular mechanism is still unknown (33).

CMV, MEMORY INFLATION AND T CELL SENESCENCE

Asymptomatic human CMV (HCMV) infection is present in most of the human population, and T cell response to HCMV is sustained and amplified over time. Consequently, the HCMV-specific T cell population acquires dominance in the peripheral blood of healthy elderly hosts. Among the total $CD8^+$ T cell population in elderly individuals, approximately 20% is specific to pp65, a dominant HCMV antigen (7). The expansion of HCMV-specific T cells in the elderly has been implicated in relation to immunosenescence. The concept of immunosenescence was first used to describe the age-associated deterioration of immune functions, characterized by functional and phenotypic changes at both cellular and systemic levels (34,35). Although it is unclear whether HCMV is the main causative agent of systemic immunosenescence, HCMV is one of the most important antigens that induce repetitive T cell stimulation, which is a powerful driving factor of immunosenescence (36,37). In addition, HCMV-specific inflationary T cells possess rather similar phenotypic and functional features to those of replicative senescent T cells. In the elderly, a majority of HCMV-specific $CD8^+$ T cells are $CD45RA^+$ effector memory cells, representing the typical phenotypic feature of terminally differentiated, replicative senescent T cells that gain CD57 and lose CD28, CCR7, and IL-7Rα expression (38-40). The $CD45RA^+$ effector memory cell population gradually expands with age and comprises more than half of the total memory $CD8^+$ T cell population, even in healthy elderly individuals (38). Considering the oligoclonality of these cells along with shortened telomere length due to extensive cell division, frequently encountered antigens, such as latent or persistent chronic viruses, are considered as major contributors to the expansion of $CD45RA^+$ effector memory T cells (36). Among these viruses, CMV has been extensively investigated in the context of immunosenescence (7,41-43).

The clinical significance of HCMV-specific T cell inflation with ageing is supported only by circumstantial evidence. CMV seropositivity and the clonal expansion of CMV-specific $CD8^+$ T cells were identified as the major immune risk phenotype (IRP) in a longitudinal study in the elderly (44). In addition, latent HCMV infection has been associated with reduction in life span (7,45), acceleration of tumor growth (46,47) and occurrence of cardiovascular diseases (48). Further studies are necessary to understand the role of memory T cell inflation in health and diseases, particularly in the senior population.

Conclusions and prospects

'Memory inflation' is a term describing progressive expansion of virus-specific $CD8^+$ T cells, particularly in the context of chronic latent CMV infection. The expanded CMV-specific $CD8^+$ T cell population is extraordinarily large and is more prominent in the elderly. Inflationary $CD8^+$ T cells possess rather similar phenotypic and functional features to those of replicative senescent T cells. Until now, the detailed nature of CMV-specific T cell responses has been explored mainly using mouse models. However, there is a concern for the discrepancies of longevity and genetic backgrounds between mice and humans, which result in an incomplete picture for elucidating CMV-specific T cell responses and immunosenescence. Non-human primates share closer developmental and evolutionary relationships to humans. Therefore, non-human primates may be a more suitable alternative as CMV animal models to understand memory T cell inflation (49). Moreover, it is necessary to dissect the roles and characteristics of inflationary T cells induced by HCMV infection. The mechanism by which inflationary T cells contribute to the pathogenesis of geriatric diseases requires further investigation.

ACKNOWLEDGEMENTS

This work was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI13C1263). This work was also supported by National Research Foundation grants (NRF-2012-M3C1A1-048860 and NRF-2014R1A2A1A10053662) and by the Korea Advanced Institute of Science and Tech-

nology (KAIST) Future Systems Healthcare Project, which is funded by the Ministry of Science, ICT and Future Planning of Korea.

CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

REFERENCES

1. Sierro, S., R. Rothkopf, and P. Klenerman. 2005. Evolution of diverse antiviral CD8$^+$ T cell populations after murine cytomegalovirus infection. *Eur. J. Immunol.* 35: 1113-1123.
2. Munks, M. W., K. S. Cho, A. K. Pinto, S. Sierro, P. Klenerman, and A. B. Hill. 2006. Four distinct patterns of memory CD8 T cell responses to chronic murine cytomegalovirus infection. *J. Immunol.* 177: 450-458.
3. Snyder, C. M., K. S. Cho, E. L. Bonnett, D. S. van, G. R. Shellam, and A. B. Hill. 2008. Memory inflation during chronic viral infection is maintained by continuous production of short-lived, functional T cells. *Immunity* 29: 650-659.
4. O'Hara, G. A., S. P. Welten, P. Klenerman, and R. Arens. 2012. Memory T cell inflation: understanding cause and effect. *Trends Immunol.* 33: 84-90.
5. Koch, S., A. Larbi, D. Ozcelik, R. Solana, C. Gouttefangeas, S. Attig, A. Wikby, J. Strindhall, C. Franceschi, and G. Pawelec. 2007. Cytomegalovirus infection: a driving force in human T cell immunosenescence. *Ann. N. Y. Acad. Sci.* 1114: 23-35.
6. Gillespie, G. M., M. R. Wills, V. Appay, C. O'Callaghan, M. Murphy, N. Smith, P. Sissons, S. Rowland-Jones, J. I. Bell, and P. A. Moss. 2000. Functional heterogeneity and high frequencies of cytomegalovirus-specific CD8(+) T lymphocytes in healthy seropositive donors. *J. Virol.* 74: 8140-8150.
7. Khan, N., N. Shariff, M. Cobbold, R. Bruton, J. A. Ainsworth, A. J. Sinclair, L. Nayak, and P. A. Moss. 2002. Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. *J. Immunol.* 169: 1984-1992.
8. Lang, K. S., A. Moris, C. Gouttefangeas, S. Walter, V. Teichgraber, M. Miller, D. Wernet, K. Hamprecht, H. G. Rammensee, and S. Stevanovic. 2002. High frequency of human cytomegalovirus (HCMV)-specific CD8$^+$ T cells detected in a healthy CMV-seropositive donor. *Cell. Mol. Life Sci.* 59: 1076-1080.
9. Holtappels, R., M. F. Pahl-Seibert, D. Thomas, and M. J. Reddehase. 2000. Enrichment of immediate-early 1 (m123/pp89) peptide-specific CD8 T cells in a pulmonary CD62L(lo) memory-effector cell pool during latent murine cytomegalovirus infection of the lungs. *J. Virol.* 74: 11495-11503.
10. Karrer, U., S. Sierro, M. Wagner, A. Oxenius, H. Hengel, U. H. Koszinowski, R. E. Phillips, and P. Klenerman. 2003. Memory inflation: continuous accumulation of antiviral CD8$^+$ T cells over time. *J. Immunol.* 170: 2022-2029.
11. Arens, R., P. Wang, J. Sidney, A. Loewendorf, A. Sette, S. P. Schoenberger, B. Peters, and C. A. Benedict. 2008. Cutting edge: murine cytomegalovirus induces a polyfunctional CD4 T cell response. *J. Immunol.* 180: 6472-6476.
12. Northfield, J., M. Lucas, H. Jones, N. T. Young, and P. Klenerman. 2005. Does memory improve with age? CD85j (ILT-2/LIR-1) expression on CD8 T cells correlates with 'memory inflation' in human cytomegalovirus infection. *Immunol. Cell Biol.* 83: 182-188.
13. Day, C. L., D. E. Kaufmann, P. Kiepiela, J. A. Brown, E. S. Moodley, S. Reddy, E. W. Mackey, J. D. Miller, A. J. Leslie, C. DePierres, Z. Mncube, J. Duraiswamy, B. Zhu, Q. Eichbaum, M. Altfeld, E. J. Wherry, H. M. Coovadia, P. J. Goulder, P. Klenerman, R. Ahmed, G. J. Freeman, and B. D. Walker. 2006. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature* 443: 350-354.
14. Hertoghs, K. M., P. D. Moerland, S. A. van, E. B. Remmerswaal, S. L. Yong, P. J. van de Berg, S. M. van Ham, F. Baas, B. ten, I, and R. A. van Lier. 2010. Molecular profiling of cytomegalovirus-induced human CD8$^+$ T cell differentiation. *J. Clin. Invest* 120: 4077-4090.
15. Smith, C. J., H. Turula, and C. M. Snyder. 2014. Systemic hematogenous maintenance of memory inflation by MCMV infection. *PLoS Pathog.* 10: e1004233.
16. Ouyang, Q., W. M. Wagner, A. Wikby, S. Walter, G. Aubert, A. I. Dodi, P. Travers, and G. Pawelec. 2003. Large numbers of dysfunctional CD8$^+$ T lymphocytes bearing receptors for a single dominant CMV epitope in the very old. *J. Clin. Immunol.* 23: 247-257.
17. Turula, H., C. J. Smith, F. Grey, K. A. Zurbach, and C. M. Snyder. 2013. Competition between T cells maintains clonal dominance during memory inflation induced by MCMV. *Eur. J. Immunol.* 43: 1252-1263.
18. Klenerman, P., and A. Hill. 2005. T cells and viral persistence: lessons from diverse infections. *Nat. Immunol.* 6: 873-879.
19. Lang, A., J. D. Brien, and J. Nikolich-Zugich. 2009. Inflation and long-term maintenance of CD8 T cells responding to a latent herpesvirus depend upon establishment of latency and presence of viral antigens. *J. Immunol.* 183: 8077-8087.
20. Redeker, A., S. P. Welten, and R. Arens. 2014. Viral inoculum dose impacts memory T-cell inflation. *Eur. J. Immunol.* 44: 1046-1057.
21. Holtappels, R., C. O. Simon, M. W. Munks, D. Thomas, P. Deegen, B. Kuhnapfel, T. Daubner, S. F. Emde, J. Podlech, N. K. Grzimek, S. A. Oehrlein-Karpi, A. B. Hill, and M. J. Reddehase. 2008. Subdominant CD8 T-cell epitopes account for protection against cytomegalovirus independent of immunodomination. *J. Virol.* 82: 5781-5796.
22. Munks, M. W., M. C. Gold, A. L. Zajac, C. M. Doom, C. S. Morello, D. H. Spector, and A. B. Hill. 2006. Genome-wide analysis reveals a highly diverse CD8 T cell response to murine cytomegalovirus. *J. Immunol.* 176: 3760-3766.
23. Sylwester, A. W., B. L. Mitchell, J. B. Edgar, C. Taormina, C. Pelte, F. Ruchti, P. R. Sleath, K. H. Grabstein, N. A. Hosken, F. Kern, J. A. Nelson, and L. J. Picker. 2005. Broadly targeted human cytomegalovirus-specific CD4$^+$ and CD8$^+$ T cells dominate the memory compartments of exposed subjects. *J. Exp. Med.* 202: 673-685.
24. Snyder, C. M., J. E. Allan, E. L. Bonnett, C. M. Doom, and A. B. Hill. 2010. Cross-presentation of a spread-defective MCMV is sufficient to prime the majority of virus-specific CD8$^+$ T cells. *PLoS One* 5: e9681.

25. Torti, N., S. M. Walton, T. Brocker, T. Rulicke, and A. Oxenius. 2011. Non-hematopoietic cells in lymph nodes drive memory CD8 T cell inflation during murine cytomegalovirus infection. *PLoS Pathog.* 7: e1002313.
26. Arens, R., and S. P. Schoenberger. 2010. Plasticity in programming of effector and memory CD8 T-cell formation. *Immunol. Rev.* 235: 190-205.
27. Arens, R., A. Loewendorf, A. Redeker, S. Sierro, L. Boon, P. Klenerman, C. A. Benedict, and S. P. Schoenberger. 2011. Differential B7-CD28 costimulatory requirements for stable and inflationary mouse cytomegalovirus-specific memory CD8 T cell populations. *J. Immunol.* 186: 3874-3881.
28. Humphreys, I. R., A. Loewendorf, T. C. de, K. Schneider, C. A. Benedict, M. W. Munks, C. F. Ware, and M. Croft. 2007. OX40 costimulation promotes persistence of cytomegalovirus-specific CD8 T Cells: A CD4-dependent mechanism. *J. Immunol.* 179: 2195-2202.
29. Humphreys, I. R., S. W. Lee, M. Jones, A. Loewendorf, E. Gostick, D. A. Price, C. A. Benedict, C. F. Ware, and M. Croft. 2010. Biphasic role of 4-1BB in the regulation of mouse cytomegalovirus-specific CD8(+) T cells. *Eur. J. Immunol.* 40: 2762-2768.
30. Bachmann, M. F., P. Wolint, S. Walton, K. Schwarz, and A. Oxenius. 2007. Differential role of IL-2R signaling for $CD8^+$ T cell responses in acute and chronic viral infections. *Eur. J. Immunol.* 37: 1502-1512.
31. Feau, S., R. Arens, S. Togher, and S. P. Schoenberger. 2011. Autocrine IL-2 is required for secondary population expansion of CD8(+) memory T cells. *Nat. Immunol.* 12: 908-913.
32. van Leeuwen, E. M., G. J. de Bree, E. B. Remmerswaal, S. L. Yong, K. Tesselaar, B. ten, I, and R. A. van Lier. 2005. IL-7 receptor alpha chain expression distinguishes functional subsets of virus-specific human $CD8^+$ T cells. *Blood* 106: 2091-2098.
33. Jones, M., K. Ladell, K. K. Wynn, M. A. Stacey, M. F. Quigley, E. Gostick, D. A. Price, and I. R. Humphreys. 2010. IL-10 restricts memory T cell inflation during cytomegalovirus infection. *J. Immunol.* 185: 3583-3592.
34. Linton, P. J., and K. Dorshkind. 2004. Age-related changes in lymphocyte development and function. *Nat. Immunol.* 5: 133-139.
35. Walford, R. L. 1969. Immunologic aspects of aging. *Klin. Wochenschr.* 47: 599-605.
36. Akbar, A. N., and J. M. Fletcher. 2005. Memory T cell homeostasis and senescence during aging. *Curr. Opin. Immunol.* 17: 480-485.
37. Pawelec, G., E. Derhovanessian, A. Larbi, J. Strindhall, and A. Wikby. 2009. Cytomegalovirus and human immunosenescence. *Rev. Med. Virol.* 19: 47-56.
38. Czesnikiewicz-Guzik, M., W. W. Lee, D. Cui, Y. Hiruma, D. L. Lamar, Z. Z. Yang, J. G. Ouslander, C. M. Weyand, and J. J. Goronzy. 2008. T cell subset-specific susceptibility to aging. *Clin. Immunol.* 127: 107-118.
39. Cavanagh, M. M., Q. Qi, C. M. Weyand, and J. J. Goronzy. 2011. Finding balance: T cell regulatory receptor expression during aging. *Aging Dis.* 2: 398-413.
40. Derhovanessian, E., A. Larbi, and G. Pawelec. 2009. Biomarkers of human immunosenescence: impact of Cytomegalovirus infection. *Curr. Opin. Immunol.* 21: 440-445.
41. Fulop, T., A. Larbi, and G. Pawelec. 2013. Human T cell aging and the impact of persistent viral infections. *Front. Immunol.* 4: 271.
42. Pawelec, G., A. Akbar, C. Caruso, R. Effros, B. Grubeck-Loebenstein, and A. Wikby. 2004. Is immunosenescence infectious? *Trends Immunol.* 25: 406-410.
43. Pawelec, G. 2014. Immunosenenescence: role of cytomegalovirus. *Exp. Gerontol.* 54: 1-5.
44. Wikby, A., F. Ferguson, R. Forsey, J. Thompson, J. Strindhall, S. Lofgren, B. O. Nilsson, J. Ernerudh, G. Pawelec, and B. Johansson. 2005. An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 60: 556-565.
45. Savva, G. M., A. Pachnio, B. Kaul, K. Morgan, F. A. Huppert, C. Brayne, and P. A. Moss. 2013. Cytomegalovirus infection is associated with increased mortality in the older population. *Aging Cell* 12: 381-387.
46. Rahbar, A., A. Orrego, I. Peredo, M. Dzabic, N. Wolmer-Solberg, K. Straat, G. Stragliotto, and C. Soderberg-Naucler. 2013. Human cytomegalovirus infection levels in glioblastoma multiforme are of prognostic value for survival. *J. Clin. Virol.* 57: 36-42.
47. Wolmer-Solberg, N., N. Baryawno, A. Rahbar, D. Fuchs, J. Odeberg, C. Taher, V. Wilhelmi, J. Milosevic, A. A. Mohammad, T. Martinsson, B. Sveinbjornsson, J. I. Johnsen, P. Kogner, and C. Soderberg-Naucler. 2013. Frequent detection of human cytomegalovirus in neuroblastoma: a novel therapeutic target? *Int. J. Cancer* 133: 2351-2361.
48. Wall, N. A., C. D. Chue, N. C. Edwards, T. Pankhurst, L. Harper, R. P. Steeds, S. Lauder, J. N. Townend, P. Moss, and C. J. Ferro. 2013. Cytomegalovirus seropositivity is associated with increased arterial stiffness in patients with chronic kidney disease. *PLoS One* 8: e55686.
49. Cicin-Sain, L., A. W. Sylwester, S. I. Hagen, D. C. Siess, N. Currier, A. W. Legasse, M. B. Fischer, C. W. Koudelka, M. K. Axthelm, J. Nikolich-Zugich, and L. J. Picker. 2011. Cytomegalovirus-specific T cell immunity is maintained in immunosenescent rhesus macaques. *J. Immunol.* 187: 1722-1732.