Can bystander activation of T cells be potent enough to activate pre-existing autoreactive T cells and so cause tissue damage and clinical disease? This old concept has been addressed in the past with an experimental transgenic mouse model also involving LCMV and VV. High frequencies of CTLs (90% of $CD8^+$ T cells) specific for a neo-antigen expressed in pancreatic islets were insufficient to cause diabetes when they were activated in a "bystander-like" manner, despite substantial cytotoxic activity *ex vivo*[10]. These results suggest that unless bystander-induced CTL activation exceeds a critical threshold, which may be very high, organ damage does not occur.

As the host matures, diverse pathogenic challenges to the immune system could help to shape the composition of the T cell memory pool by causing proliferation[1] and "attrition"[11]. In all these experiments, it is also important to recognize that CTLs can be preferentially sequestered or "compartmentalized", confounding attempts to measure the total memory CTL pool[12].

Overall, the responses reported by Chen *et al.* are examples of the "fuzziness" evident in the logic of the immune system. Although the results these researchers found in manipulating the immune response do not represent classical memory, they resemble "memory-like effects", which may become apparent when multiple antigens are encountered sequentially. Perhaps what these antiviral T cells experience is not so much total recall as a case of *déjà vu*.

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[1]Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford OX3 9DU, UK. [2]The Peter Medawar Building for Pathogen Research, University of Oxford, South Parks Road, Oxford OX1 3SY, UK. (Rodney.Phillips@ndm.ox.ac.uk)

Cytomegalovirus: from evasion to suppression?

PAUL J. LEHNER[1] AND GAVIN W. G. WILKINSON[2]

Viruses, such as CMV, have evolved a number of strategies with which to evade the immune system. Evidence is now emerging that murine CMV can also suppress the immune response by inducing functional paralysis of DCs.

Dendritic cells (DCs) are the professional antigen-presenting cells within the immune system and have emerged as key players in initiating the T cell response to viral infection[1]. This is, in part, related to their apparently unique capacity to prime naïve T cells and thus trigger differentiation of an activated effector T cell population. Uptake and processing of antigen is carried out by immature DCs that reside in peripheral tissues, where they express a panoply of receptors that allow them to respond to microbial products or pro-inflammatory stimuli. The recognition of such signals triggers the differentiation of immature DCs into mature DCs, which have a dramatically altered function. Mature DCs have a reduced capacity for antigen uptake, but express high amounts of major histocompatibility complex (MHC) as well as costimulatory molecules, which makes them excellent presenters of antigen to T cells. This maturation process is associated with altered expression of chemokine receptors that facilitates mature DC migration to the T cell areas of lymph nodes. The crucial role played by DCs in orchestrating the T cell response makes them an attractive and vulnerable target to viral attack. In this issue of *Nature Immunology*, Andrews and colleagues examine the consequences of murine cytomegalovirus (MCMV) infection on both *in vitro* and *in vivo* DC function[2]. They show that MCMV is able to both infect and induce a functional paralysis of murine DCs. This may represent yet another powerful mechanism by which MCMV manipulates the immune response.

Viral infection of DCs may be associated with two potential outcomes. Influenza infection causes DC maturation and the release of interleukin 12 (IL-12); this results in the induction of an extremely effective immune response[3]. However, an increasing number of viruses may actually impair antigen presentation, as has been reported for measles, HIV, vaccinia virus, dengue virus, venezuelan equine encephalitis virus, herpes simplex virus, smallpox and lymphocytic choriomeningitic virus (LCMV)[4]. Andrews and colleagues now show that MCMV firmly belongs within this latter grouping. As a herpesvirus, MCMV has been effectively exploited as a model system for human CMV (HCMV) infection and, indeed, persistent virus infections in general. However, caution should be exercised: one must not over-extrapolate from the MCMV animal model to HCMV disease because there are marked differences in the viral pathology of these infections and the degree of sequence similarity between the two genomes is surprisingly low[5]. HCMV has become a paradigm for viral immune evasion, and both HCMV and MCMV encode an elaborate array of immune-evasion strategies[6] (**Table 1**). Although it is clear that the viruses appear to adopt similar strategies, the mechanisms are not identical. This reflects the coevolution of each virus with its host: for example, HCMV and MCMV both encode multiple genes that interfere with MHC class I antigen presentation, but act at different stages in the pathway.

The specter now being raised is not merely that of immune evasion but of active suppression of the immune system mediated by impairment of DC function. Andrews and colleagues demonstrate productive infection of murine DCs with MCMV both *in vitro* and *ex vivo*. MCMV infection is associated with initial DC activation, followed by reduced expression of MHC as well as costimulatory molecules that are critical for T cell maturation. The infected DCs lose the capacity to secrete IL-12 or IL-2, which contributes to their functional paralysis. In addition, infected DCs remain unresponsive to additional maturation stimuli, such as lipopolysaccharide (LPS), and are unable to prime an effective T cell response. Therefore, prevention of the terminal stages of DC differentiation could result in inefficient presentation

Table 1. Immune evasion genes of HCMV and MCMV

Function	HCMV gene	MCMV gene
Down-regulation of MHC class I	US2, US3, US6, US11	m4, m6, m152
Down-regulation of MHC class II US2	–	
MHC class I homolog	UL18	m144
NK cell evasion	UL40, UL16	–
Chemokine receptor	US28	M33
Additional 7TM receptors	UL33, UL78, US27,	M78
TNFR homolog	UL144	–
IL-10 homolog	UL111a	–
vChemokine	UL146	M131
Inhibitors of apoptosis	UL36, UL 37	–

of MCMV as well as other unrelated antigens.

The fate of HCMV in DCs is clearly a matter of great interest. The experiments done with the MCMV model deal with acute infection in which systemic MCMV infection resulted in an overwhelming attack on DCs, with more than 70% of splenic DCs infected 48 h after infection. At the earliest phase of a primary infection, targeting of DCs by MCMV may both subvert the immune system and allow infected cells to migrate to lymph nodes and effectively disseminate the virus, as has been observed after HIV infection[7]. A proposed site of HCMV latency is a subset of $CD34^+$ myeloid progenitors; it is envisaged that reactivation follows differentiation into cells of the myeloid lineage, including a subset of macrophages that display DC markers[8]. Such a strategy for a persistent virus to reactivate in professional antigen-presenting cells was unexpected—but perhaps astute—if HCMV, like MCMV, also disables the maturation steps associated with antigen processing. Data suggest that, at least *in vitro*, human immature DCs are indeed susceptible to infection with HCMV clinical isolates, although they are not susceptible to the commonly used AD169 and Towne laboratory strains. The ensuing situation appears to parallel that seen with MCMV, as productive HCMV infection decreases cell surface expression of MHC class I and II, CD40 and CD80 on immature DCs[9] and inhibits the LPS-induced maturation of surface DC markers as well as IL-12 and tumor necrosis factor-α (TNF-α) production (M. Moutaftsi, A. Mehl, L. Borysiewicz and S. Tabi, unpublished data). In both the murine and human systems, only the immature DCs are susceptible to infection and, following maturation, DCs acquire resistance to their respective viruses.

With the possible exception of HIV, the human $CD8^+$ cytotoxic T lymphocyte (CTL) response to CMV surpasses that observed in response to any other pathogen; it is focused on two immunodominant antigens (pp65 and IE1)[10]. In addition, a robust MCMV-specific CTL response is protective after MCMV infection *in vivo*[11]. If both human and murine CMV can infect and prevent DC maturation, how is the well documented virus-specific CTL response generated? Andrews and colleagues have not yet addressed this issue and it will be important to determine whether their reported DC tropism of MCMV is applicable to other strains, identify which DC subsets are infected and determine whether DC infection prevents endogenous presentation of MCMV-specific antigens to T cells. After murine LCMV infection, the ability of the virus to infect and replicate in splenic DCs is a key factor in establishing persistent infection. LCMV strains that have a preferential tropism for DCs, due to high-affinity binding to the cellular receptor, cause a suppression of the immune response[12]. The decrease in cell surface MHC class I expression seen after HCMV infection, which results from the combined actions of HCMV US2, US3 US6 and US11 together with impaired DC function, also raises the question as to how the CTL response is generated and its effectiveness in combating HCMV infection. Cross-presentation of HCMV antigens enables noninfected DCs to stimulate and promote $CD8^+$ T cell responses[13]; however, the role played by cross-presentation *in vivo* has not been assessed.

For the majority of immune-evasion strategies by CMV (**Table 1**) it has been possible to assign a CMV-encoded gene with a distinct subversive function. Lytic virus infection, as seen after CMV infection of DCs, is clearly traumatic and induces gross perturbation of the infected cell. It is possible that impairment of DC function and maturation observed during CMV infection may be a nonspecific consequence of viral replication. However, because HCMV and MCMV are well adapted viruses that enjoy a sophisticated relationship with their respective hosts, it may be possible to identify specific viral gene(s) that specifically inhibit DC maturation. The rapid generation of banks of CMV mutants using bacterial artificial chromosome technology will permit such issues to be addressed.

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[1]Division of Immunology, Cambridge Institute of Medical Research, Addenbrookes Hospital, Hills Rd, Cambridge CB2 2XY, UK. (pjl30@cam.ac.uk) [2]Section of Infection and Immunity, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XX, UK. (wilkinsongw1@cardiff.ac.uk)