Flavivirus-Induced Up-regulation of MHC Class I Antigens; Implications for the Induction of CD8⁺ T-Cell-Mediated Autoimmunity

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INTRODUCTION

Modulation of the major histocompatibility complex (MHC) class I antigen processing and presentation pathway is induced upon infection by members of a number of virus families (Maudsley & Pound 1991, Müllbacher 1992). The effect is, in most instances, a down-regulation of MHC class I cell-surface expression. This may be caused by a down-regulation of biosynthesis of the class I restriction elements or a general shut down of host protein synthesis (Schneider & Shenk 1987, Townsend et al. 1988), inhibition of the function of the peptide transporters for MHC class I antigen presentation (TAP) (Rotem-Yehudar et al. 1994, York et al. 1994, Früh et al. 1995, Hill et al. 1995), or prevention of assembly and transport of class I MHC molecules (Beersma et al. 1993, Browne et al. 1990, Burgert et al. 1987, del Val et al. 1992, Warren et al. 1994). This host–pathogen interaction is frequently seen during infections that result in virus persistence, and underlines the important role that MHC class I-restricted cytotoxic T (Tc) cells play in virus clearance by recognition of infected cells. In view of this effective immune mechanism it appears paradoxical that infection with some viruses should result in the up-regulation of MHC class I cell-surface expression. This effect has been noted on cells with naturally low MHC class I cell-surface expression (astrocytes, oligodendrocytes, trophoblasts) during infections with measles virus, mouse hepatitis virus, herpes simplex virus and flavi...
viruses (Suzumura et al. 1986, Massa et al. 1987, King et al. 1989, Liu et al. 1989, Pearce et al. 1994, Pereira et al. 1994, Gilmore et al. 1994). In addition, flaviviruses infection also increases MHC class I expression in a wide range of other cell types. This general effect is consistent with the mechanism by which flaviviruses infection augments MHC class I cell surface expression, which involves a TAP-independent supply of peptides from the cytoplasm to the lumen of the endoplasmic reticulum for assembly with MHC class I molecules (Müllbacher & Lobigs 1995). Here we review the implications of this host-pathogen interaction for the Tc cell immune response.

FLAVIVIRUS IMMUNOBIOLOGY

Flavivirus molecular biology, pathogenesis and immunity have been reviewed in detail elsewhere (Chambers et al. 1990, Hill et al. 1993a, Monath & Heinz 1996, Rice 1996).

Flaviviruses are small, positive-strand RNA viruses. The genome (approximately 11 kb in length) encodes a single polyprotein that is processed by host and viral proteinases into at least 10 viral proteins. Flaviviral particles assemble intracellularly probably by association of the viral nucleocapsid with endoplasmic reticulum (ER) membranes modified by viral surface proteins (Rice 1996). The flaviviral envelope protein is the dominant target antigen for the virus-neutralizing and protective humoral immune response (Monath & Heinz 1996). The flavivirus structural proteins are also the source of T-helper cell determinants (Rothman et al. 1989, Kulkarni et al. 1992, Leclerc et al. 1993, Roehrig et al. 1994), whereas the Tc cell response is almost exclusively directed against peptide determinants from the non-structural polyprotein domain (Hill et al. 1993b, Rothman et al. 1993, Lobigs et al. 1994, Livingston et al. 1995).

The flaviviral natural transmission cycle requires, for most members of this virus family, the replication in an arthropod vector (usually mosquitoes or ticks) and a vertebrate host. Many flaviviruses are associated with disease in humans (Monath & Heinz 1996). Of particular public health concern are the flavivirus-type species yellow fever virus (YF) and the dengue viruses (Den), which are responsible for widespread human epidemics of haemorrhagic fever in tropical and subtropical areas, and Japanese encephalitis virus (JE), which annually causes large outbreaks of encephalitis in humans in wide areas of Asia. The live attenuated YF vaccine (17D) has been spectacularly successful in preventing major outbreaks of yellow fever over the last 50 years; on the other hand there is an urgent requirement for a Den vaccine and an improved vaccine against JE (Monath 1994, Monath & Heinz 1996).

The cytolytic leucocyte-target cell interaction after flavivirus infection-induced up-regulation of MHC class I

The two main cytolytic effector leucocyte populations, natural killer (NK) and Tc cells, which are important in the control of viral infections (Blanden 1974, Bu-
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Mock

IFN

WNV

Figure 1. Flavivirus- and \( \gamma \)-interferon (\( \gamma \)-IFN)-induced up-regulation of MHC class I on mouse embryo fibroblasts (MEF). MEF from CBA mice were infected with 20 plaque-forming units (PFU)/cell of West Nile virus (WNV), treated with 500 U \( \gamma \)-IFN, or mock-infected for 36 h. Cells were stained with fluorescein isothiocyanate (FITC) after incubation with primary antibody (mAb). mAb HB-160 (ATCC) was used for H-2K\(^{\text{b}}\) specific staining.

Kowalski et al. 1985), have been shown to have an inverse relationship in their lytic activity and the level of cell-surface MHC class I expression (Müllbacher & King 1989). Tc cells lyse target cells more efficiently with increased MHC class I expression (Shimonkevitz et al. 1985, King et al. 1986), especially in a response to allogeneic MHC class I. NK cells as a rule lyse target cells with low MHC class I better than cells with high expression (Trinchieri & Santoli 1978, Pointek et al. 1985, Müllerbacher & King 1989).

The modulation of Tc and NK cell target recognition after flavivirus infection can be demonstrated using mouse embryo fibroblasts (MEF), a cell population with low to moderate MHC class I expression (King et al. 1986). Figure 1 shows the pronounced increase of class I MHC after West Nile virus (WNV) infection of CBA MEF, which surpasses that seen with the classic inducer of MHC class I, \( \gamma \)-interferon (\( \gamma \)-IFN). The effect this has on the lytic activity of Tc and NK cells is shown in Table I. Two Tc cell populations were used: secondary WNV-immune Tc cells generated in vitro and BALB/c anti-CBA (anti-H-2\(^{\text{b}}\)) allogeneic Tc cells. The WNV-immune Tc cells lysed the WNV-infected targets efficiently but did not lyse \( \gamma \)-IFN-treated targets. Alloreactive Tc cells killed targets infected with WNV, or treated with \( \gamma \)-IFN, more efficiently than mock-infected targets. Conversely, NK
cells lysed mock-infected and vaccinia virus (VV)-infected targets to a greater extent than the WNV-infected targets.

**Flavivirus infection augments the supply of peptides to the ER independently of the peptide transporters**

We have recently addressed the mechanism by which flavivirus infection induces the up-regulation of cell-surface expression of MHC class I (Müllbacher & Lobigs 1995). We found that functional peptide transporters (TAP), which supply peptides from the cytoplasm to the lumen of the ER for assembly with MHC class I molecules, are not required for this virus-induced effect. Infection of a TAP-deficient cell line (RMA-S) and Syrian hamster cell lines (BHK and NIL-2), which are restrictive in TAP-dependent peptide transport (Lobigs et al. 1995), with flaviviruses of the JE serocomplex [WNV, Kunjin virus (KUN), JE and Murray Valley encephalitis virus (MVE)] resulted in the augmentation of plasma membrane expression of MHC class I molecules, whereas the expression of other cell-surface markers was not increased (Müllbacher & Lobigs 1995).

Here we demonstrate that infection with Den and YF also induces the up-regulation of MHC class I cell-surface expression. Flow cytometry profiles of RMA (wild-type TAP phenotype) and RMA-S cells uninfected or infected for 48 h with Den, YF (17D vaccine strain) or WNV and stained for H-2K^b cell-surface expres-
Figure 2. YF, Den and WNV mediate up-regulation of MHC class I on TAP-deficient RMA-S and wild-type RMA cells. RMA-S (A) and RMA (B) cells were infected with 20 PFU/cell of WNV (-), 20 PFU/cell of YF (--), 20 PFU/cell of Den (---) or mock-infected (shaded histogram) for 36 h. Cells were FITC-stained after incubation with primary antibody. mAb HB41 (ATCC) was used for H-2K^b-specific staining.
sion are shown in Fig. 2A, B. The MHC class I-specific staining was increased to a similar extent (two- to fourfold) in these two mouse lymphoblastoid cell lines by infection with the three flaviviruses. The same flaviviruses also caused an increase in class I MHC expression on human cells (Bao et al. 1992, Müllerbacher et al. unpublished results). Flavivirus infection also induced the presentation of a range of T-cell peptide determinants in TAP-deficient cell lines when used as target cells for virus-immune and alloreactive Tc cells. Thus infection with flaviviruses could partially complement the defect in MHC class I cell-surface expression and antigen presentation in TAP-deficient cells, suggesting that peptide supply across the ER membrane is induced by a route different from that of the peptide transporter pathway. We have speculated that this may be a consequence of the mechanism of flavivirus assembly, which takes place at the membranes of the ER. It has not been established whether other viruses that assemble intracellularly at the ER or early Golgi membranes, e.g. rotaviruses, coronaviruses, pestiviruses and rubella virus (Petersson 1991, Krijnse-Locker et al. 1994, Holmes & Lai 1996), can also increase MHC class I antigen presentation and cell-surface expression.

Tc cell memory in mice infected with flaviviruses

In general, acute viral infection of mice provokes a primary Tc cell response that peaks within a few days of the peak of viral load in infected tissues and then declines following viral clearance (Blanden 1974). This primary response peak is usually within the first week after infection, depending upon the kinetics of viral spread and growth. Memory Tc cells, defined by enhanced kinetics of induction in vivo (Effros et al. 1978, Müllerbacher & Tha Hla 1993) and increased reactivity to virus-infected cells in vitro (Gardner & Blanden 1976, Kesson et al. 1988), are detectable in lymphoid tissues of virus-infected mice from the time the primary response becomes established, and usually persist for the lifespan of the mouse (Müllerbacher & Blanden 1978, Ashman 1982) in the absence of persisting infected cells (Müllerbacher 1994). When virus-immune Tc cell precursors are cultured for 5 days in vitro in the presence of virus-infected, MHC class I-matched stimulator cells, the expected strong cytotoxic activity against virus-infected, MHC class I-matched target cells is sometimes accompanied by cytotoxic activity against uninfected control targets (Kesson et al. 1988). This phenomenon (mediated by CD8+ T cells; Müllerbacher, unpublished data) is striking in the case of flaviviruses (Fig. 3A). We have determined empirically that consistent flavivirus-specific target cell lysis in the absence of high lysis of uninfected targets is only achieved with secondary, flavivirus-immune Tc cells generated by in vitro stimulation of splenocytes taken 6–14 days after priming of mice with flaviviruses. The high self-reactivity of memory flavivirus-immune secondary Tc cells is apparently a consequence of the biology of flavivirus infection and does not involve mimicry of MHC class I-presented self-peptides by the viral peptide determinants that induce Tc cell responses. Flavivirus Tc cell peptide determinants are predominantly derived from the non-structural domain of the virus polyprotein.
Figure 3. Kinetics of priming for Tc cell recall response in vitro to WNV. CBA mice were immunized with 5 × 10^6 PFU WNV(A) or 10^7 PFU W-1024 expressing the Kunjin virus (KUN) non-structural polyprotein region (B). Spleens from mice primed for different lengths of time were restimulated in vitro for 5 days with syngeneic splenocytes infected with 1–5 PFU/cell of WNV. Effectors were tested for lytic activity on L929 target cells infected for 36 h with 20 PFU/cell of WNV (open bars) or mock-infected (solid bars). % specific lysis is derived from a fourfold titration curve of effector cells and solved at an effector to target ratio of 30:1 by logarithmic regression analysis.

When this entire region is encoded via a recombinant vaccinia virus (VV) (VV-1024; Hill et al. 1992) and used to prime mice, the secondary flavivirus-immune Tc cell response generated in vitro does not display the strong lysis of uninfected control target cells that follows flavivirus infection (Fig. 3B).

Following the emergence of strong lytic activity against uninfected MHC class I-matched target cells in Tc cell responses of flavivirus-primed mice, memory Tc cells reactive to flavivirus-infected target cells decline, so that by 4 weeks after infection the activity is no greater than at 1 week and substantially lower than it was at 2 weeks (Table II). This decline in Tc cell memory is also exhibited in the response to an antigenically unrelated virus in the presence of flavivirus infection in the same animal when the alpha virus, Semliki Forest virus (SFV) was used in coinfection experiments with WNV (Table II). Tc cells immune to SFV are not cross-reactive on targets infected with flaviviruses (Müllbacher et al. 1986). These data suggest that the generation of 'anti-self' activity by flavivirus infection may generally impair the maintenance of long-term Tc cell memory against co-infecting viruses. Whether long-term pre-established memory is also vulnerable to this effect needs to be explored.

Modulation of CD8^+ T cell immunity after virus-induced MHC class I up-regulation

T cells with avidity for self-antigens below the threshold of activation are present in the normal peripheral T-cell repertoire. These T cells could have matured in the
TABLE II

Flavivirus-mediated suppression of long-term Tc cell memory to an unrelated virus

| In vivo\(^b\) priming | In vitro\(^b\) boost | 7 d | 14 d | 28 d |
|------------------------|----------------------|-----|-----|-----|
| SFV                    | SFV                  | 46(35) | -     | 72(31) | 73(46) | - |
| SFV                    | SFV                  | 50(37) | -     | 68(34) | 73(42) | - |
| SFV/WNV                | SFV                  | 46(33) | -     | 59(39) | 23(9)  | - |
| SFV/WNV                | SFV                  | 30(29) | -     | 36(29) | 22(10) | - |
| WNV                    | WNV                  | -     | 17(10) | -     | 46(32) | 68(10) |
| WNV                    | WNV                  | -     | 34(12) | -     | 64(33) | 58(13) |
| SFV/WNV                | WNV                  | -     | 24(15) | -     | 70(31) | 55(19) |
| SFV/WNV                | WNV                  | -     | 19(19) | -     | 61(36) | 59(19) |

\(^a\) CBA/M mice were primed i.p. with either 10^7 PFU SFV, 5×10^6 WNV or 10^7 PFU SFV plus 5×10^6 PFU WNV.

\(^b\) Spleen cells of two individual mice primed for 7, 14 or 28 days were boosted in vitro with syngeneic splenocytes infected with SFV or WNV as has been described elsewhere (Müllbacher et al. 1986).

\(^c\) % specific lysis of SFV- or WNV-infected L929 target cells with lysis of mock-infected targets subtracted in parentheses. Values given are from a fourfold titration curve and solved at an effector to target cell ratio of 30:1 by logarithmic regression analysis.

...thymus after screening (negative selection) against self-MHC–peptide antigen complexes of a type and concentration expressed by the thymic cellular selecting elements. Activation of these peripheral T cells can occur by a change in the quantity or quality (or both) of MHC–peptide complexes. Thus the result of infection and presentation of foreign peptides and/or up-regulation of MHC class I expression (Blanden et al. 1987) could provide sufficient ligands such that even Tc cells with antigen receptors of low affinity would reach activation thresholds of avidity. Accordingly, the substantial up-regulation of MHC class I cell-surface expression induced by flavivirus infection could be a trigger for the activation of autoreactive T cells. The high self-reactivity of secondary, \textit{in vitro}, flavivirus-immune Tc cells, as reflected by high lysis of uninfected target cells, suggests that this autoreactivity occurs, perhaps transiently, \textit{in vivo}. This raises the question of why flavivirus infection of both laboratory animals and humans, following exposure to flaviruses either by insect bites or vaccination, does not trigger overt autoimmune disease. In contrast, the kinetics of Tc cell memory in mice infected with flaviviruses indicates that the Tc cell reactivity to flavivirus-infected and uninfected target cells declines beyond 2 weeks after infection. Up-regulation of self-antigen presentation due to the increased cell-surface density of MHC class I molecules on virus-infected cells in the periphery may have two outcomes, depending on whether the infected cells can provide the necessary costimulatory signal for T-cell activation. Thus a flavivi-
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Flavivirus-induced increased avidity of interaction of naive T cells with non-professional antigen-presenting cells (APC) may anergize rather than activate these T cells. Alternatively, activation would follow T-cell interaction with infected, professional APC in inflammatory sites or the lymph node microenvironment. This latter scenario could take place in the first week after flavivirus infection. Flaviviruses manifest a wide tissue tropism (Monath & Heinz 1996). The first focus of flavivirus infection in vertebrates following natural transmission by an infected insect vector is in the skin. From there the infection spreads to the regional lymph nodes via a primary viremia. This is simulated by experimental inoculation by the intravenous or intraperitoneal routes. Flavivirus replication in secondary lymphoid tissues may then constitute the environment where virus-induced up-regulation of MHC class I cell-surface expression on professional APC results in the activation of self-reactive T cells. It is plausible to suggest that this may cause a transient break in self-tolerance, as manifested by in vitro Tc cell reactivity against uninfected target cells expressing self-MHC class I. The down-regulation of this activity may in some way have a negative impact on Tc cell memory against infected self. Self-reactive Tc cells could directly kill fellow members of the T-cell pool with which they come into contact, since once activated effector Tc cells apparently demand less avidity of interaction to trigger effector function than to trigger activation (Müllbacher & Blanden 1979). A general down-regulation of the T-cell response to self- and foreign antigens occurs in other situations. Pregnancy is reported to induce a transient state of T-cell tolerance specific to the paternal alloantigen, but can also induce a remission of autoimmune disease (Waites & Whyte 1987, Tafuri et al. 1995).

Implications of flavivirus-induced MHC class I up-regulation for flavivirus vaccination

Flavivirus infection of humans and laboratory animals generates effective and longlasting protective immunity to the homologous virus. However, this immunity is essentially type-specific, consistent with virus-neutralizing antibody-based protection. Thus vaccination with the YF live attenuated vaccine does not significantly reduce the risk and severity of infection with other flaviviruses (e.g. Den or JE). Similarly infection with one strain of Den does not protect from disease induced by a heterologous serotype of Den, but rather may predispose for the more severe disease of Dengue haemorrhagic fever. This is thought to involve immune enhancement of infection of Fc receptor-bearing mononuclear phagocytes, which appear to be the principal target cell for virus replication, with a heterologous serotype of Den due to the presence of subneutralizing concentrations of dengue virus-reactive antibodies (Halstead 1988). These observations suggest that natural flavivirus infection does not give rise to a protective and flavivirus cross-reactive Tc cell memory immune response for the reasons outlined above, and in view of the broad flavivirus cross-reactivity at the level of target cell recognition of flavivirus-im-
immune secondary in vitro Tc cells (Gajdosova et al. 1981, Hill et al. 1993). Alternatively, Tc cells may not be required for the elimination of flavivirus-infected cells in vivo, which seems unlikely in view of the significance of Tc cell-mediated viral clearance in other virus infections.

We suggest that the failure of generation of cross-reactive and protective CD8+ memory Tc cells is a consequence of flavivirus-induced up-regulation of class I MHC molecules resulting in down-regulation of class I-restricted Tc cell memory. This may be of relevance for flavivirus vaccination where, in the case of a Den vaccine, simultaneous durable protective immunity to all four serotypes of Den in the absence of infection-enhancing antibodies is desirable. Using recombinant vector subunit vaccination (virus vectors or naked DNA) the problem of flavivirus-induced MHC class I up-regulation and down-regulation of Tc cell memory could be overcome. Using vaccinia virus constructs encoding the entire sequence of either the non-structural region of MVE or KUN, we have been unable to observe increased expression of MHC class I after target cell infection (Müllbacher & Lobigs, unpublished data). Moreover, we obtained long-lasting Tc cell memory to the recombinant antigen and the vector virus (Fig. 3B). The flavivirus Tc cell determinants are almost exclusively clustered in the non-structural polyprotein region. This entire fragment can be expressed in the absence of the structural proteins to fulfill the requirement of vaccination of an outbred population where multiple peptide determinants presented by the polymorphic class I MHC restriction elements are needed.

SPECULATION

The foregoing results offer a possible explanation for the lower incidence of type 1 diabetes and other autoimmune disorders in human populations living near the equator than in genetically similar populations living closer to the poles, suggesting environmental factor(s) reducing incidence near the equator or increasing it near the poles (Acheson 1977, LaPorte et al. 1985, Dean & Elian 1995). Evidence from NOD mouse colonies is that certain infectious agents (mouse hepatitis virus, a coronavirus which may up-regulate class I MHC, or Bacille Calmette–Guerin) can significantly reduce the incidence of spontaneous diabetes (Wilberz et al. 1991). Taken together, these data suggest the possibility that infection of human populations near the equator may be responsible for their lower incidence of type 1 diabetes. Candidate infections would be immunization with the live attenuated 17D strain of YF and natural infection with Den. One obvious question concerns the impact of yellow fever vaccination on long-term immunological memory against other childhood viral vaccines. If detrimental effects on memory can be avoided by appropriate timing of vaccination regimens, the potential use of 17D yellow fever vaccine more widely as a preventive agent against autoimmune diseases in general may be worth investigating.
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SUMMARY

Infection of a wide variety of cells of human, mouse and other species' origin by flaviviruses such as WNV, YF, Den, MVE, KUN and JE, increases the cell-surface expression of MHC class I. This MHC class I up-regulation is not due to increased MHC class I synthesis per se, but the result of increased peptide availability in the ER for MHC class I assembly. This is most likely due to the interaction of the viral polyprotein with the ER membrane during viral replication. Flavivirus infection can overcome peptide deficiency in TAP-deficient or non-permissive cell lines such as RMA-S and Syrian hamster cells, BHK and NIL-2. The consequence of this increased MHC class I expression manifests itself in reduced susceptibility to NK cells and augmented lysis by Tc cells. In mice, long-term flavivirus-immune Tc cell memory formation is impaired, following the appearance of strong anti-self Tc cell reactivity observed in in vitro cultures from splenocytes of flavivirus-primed animals. We hypothesize that flavivirus-induced MHC class I up-regulation leads to transient T-cell autoimmunity, followed by down-regulation of both autoimmunity and virus-specific Tc cell memory. Furthermore, we speculate that flavivirus infections of humans in the tropics may be responsible for the observed lower incidence of overt autoimmunity in these geographic regions than in temperate climates where flaviviruses are not endemic.

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