

REVIEW

Silencing T cells or T-cell silencing: concepts in virus-induced immunosuppression

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The ability to evade or suppress their host's immune response is a property of many viruses, indicating that this provides an advantage for the pathogen to spread efficiently or even to establish a persistent infection. The type and complexity of its genome and cell tropism but also its preferred type of host interaction are important parameters which define the strategy of a given virus to modulate the immune system in an optimal manner. As they take a central position in any antiviral defense, activation and function of T cells are the predominant target of almost any viral immunosuppressive regimen. In this review, we aim to summarize two different strategies whereby this could be achieved. Retroviruses can infect professional antigen-presenting cells and impair their maturation and functional properties. This coincides with differentiation and expansion of silencing T cells referred to as regulatory T cells with suppressive activity, mainly to CD8⁺ effector T cells. The second concept, outlined for measles virus, is a direct, contact-mediated silencing of T cells which acquire a transient paralytic state.

The interaction of viruses with their hosts is a dynamic, adaptive process characterized by the struggle of the latter to control and combat the infection by immune responses and in which the invading pathogen tries either to counteract or evade in order to survive and spread. Both arms of the immune system, the innate and adaptive immune systems, play important roles in protecting vertebrates against viral infections. Barriers imposed by the innate immunity, e.g. type I interferons or natural killer cells, are highly efficient and this is reflected by the fact that proteins aiming to circumvent these immune responses can be found in many viruses. However, this review will focus on the escape mechanisms of viruses from adaptive T-cell responses. Escaping control by the adaptive immunity can be achieved by various mechanisms including competing aggressively against immune control by fast replication/dissemination or generation of antigenic variants. A more sophisticated way of immune evasion is exerted efficiently by members of the *Herpesviridae*, which encode a plethora of proteins in their genomes which prevent antigen presentation. From the virus point of view, these evasion strategies provide a selective advantage for the virus itself. In contrast, viruses can also cause a generalized immunosuppression which may be required to facilitate their own spread, but will also be of advantage for opportunistic pathogens. The magnitude, targets and effector mechanisms for immunosuppression as well as its pathogenic significance certainly may differ between viruses. In the last few years, advances have been made in understanding the mechanisms of virus-induced immunosuppression. It has become obvious that there is not a single way in which viruses mediate general immunosuppression, since different mechanisms have been defined in different virus infections. In particular, more direct mechanisms of immunosuppression in which viral proteins suppress functions of immune cells have been described, as well as more indirect mechanisms in which viruses induce inhibitory cells or mediators of the immune system, which in turn suppress lymphocytes with antiviral activity. This review compares direct versus indirect mechanisms of virus-induced immunosuppression by focusing on well-characterized infections with measles virus (MV) and various retroviruses. In patients infected with retroviruses or MV, immunosuppression plays a central role in virus-induced pathology and we discuss the mechanisms that are involved. Here, MV is described as an example of viruses that inhibit T-cell activation, proliferation or viability directly by means of viral proteins. In contrast, retroviruses have recently been reported to suppress T-cell responses indirectly by inducing regulatory T cells which then act to prevent activation of effector T or B cells. Both mechanisms of virus-induced immunosuppression have to be studied in detail in order to develop new therapeutic approaches to overcome immune failure.

Retroviruses: the silencing T-cell concept

One hallmark of many retroviral infections is a severe virus-induced immunosuppression. For example, human immunodeficiency virus- (HIV-) infected patients not only develop transient immunosuppression but progress to a severe immunodeficiency during chronic infection. Many different features of this viral infection seem to contribute to the breakdown of the immune system. Firstly, HIV infects CD4-positive helper T (Th) cells and antigen-presenting cells [APCs;

macrophages and dendritic cells (DC)] and induces dysfunction and cell death in these populations. Progression to AIDS is negatively correlated with CD4⁺ T-cell numbers, indicating that the loss of Th cells is a critical step in the development of HIV-induced immunodeficiency. It is still a matter of debate whether the decrease in CD4⁺ T-cell numbers is induced solely by direct viral infection of these cells or whether indirect effects also play a role. There is evidence that apoptosis of uninfected bystander T cells and impaired thymic output of T cells might also contribute to the loss of CD4⁺ T cells (Gougeon, 2003). In addition to mechanisms leading to Th cell disappearance and immunodeficiency, HIV can also interfere with antigen presentation to T cells. For example *nef*, an accessory gene of HIV, has been reported to downregulate class I major histocompatibility complex (MHC) molecules efficiently on infected cells (Johnson & Desrosiers, 2002). As a consequence, these cells can no longer be recognized and killed by cytotoxic T lymphocytes (CTL). Furthermore, several studies have shown that mutations in T-cell epitopes occur frequently during HIV infection, leading to viral escape from T-cell activity (Goulder & Watkins, 2004). Virus-induced changes in the cytokine production of T cells have also been reported in HIV infection. From these studies it has been postulated that a Th1 to Th2 switch might contribute to HIV pathogenesis (Clerici & Shearer, 1993).

The overall relevance of the different mechanisms of HIV-induced immunosuppression and immunodeficiency mentioned above for disease progression and AIDS has not been completely understood. Several reviews have recently been published which describe and discuss these aspects of HIV immunopathogenesis in great detail (Johnson & Desrosiers, 2002; Gougeon, 2003; Goulder & Watkins, 2004). We have therefore focused on a newly described mechanism of retrovirus-mediated immunosuppression involving regulatory T cells. This indirect mechanism of viral immune evasion has been discovered in the Friend retrovirus (FV) mouse model (Iwashiro *et al.*, 2001), yet there is strong evidence that it might also play an important role in chronic viral infections in humans, including HIV infection.

Regulatory T cells in HIV infection

In addition to the direct immunosuppressive effects of HIV and its proteins, it has been reported that indirect mechanisms can also contribute to retrovirus-induced immunosuppression. One hallmark of many retroviral infections is the development of a functional impairment of T cells which are not directly infected by a virus. The features of this T-cell dysfunction and the possible role of regulatory T (Treg) cells in this immunosuppression will be the focus of the first part of this review.

Treg cells are T cells that suppress other T-cell responses (for review see Wickelgren, 2004). Several subsets of Treg cells which can be distinguished by their phenotype and function have been identified. These include natural Treg cells, which are a subset of T cells expressing the high-affinity interleukin-2 (IL-2) receptor alpha chain (CD25). These cells are known to play a central role in the maintenance of immunological homeostasis and self-tolerance in autoimmunity. In addition, pathogen-specific Treg cells are known to expand during infections and to be involved in preventing infection-induced immunopathology (Fig. 1). These cells are referred to as induced Treg cells. Induced Treg cells are able to destroy or functionally impair

effector T cells at a time point of infection when most of the pathogen has successfully been eliminated (Fig. 1). However, recent data indicate that induced Treg cells can be involved in T-cell dysfunction and impaired pathogen clearance in chronic infections. For example, functional impairment of effector CD4⁺ T-cell and CD8⁺ T-cell responses has been described for patients infected with HIV (Trimble & Lieberman, 1998; Appay *et al.*, 2000; Lieberman *et al.*, 2001; Migueles *et al.*, 2002; Hess *et al.*, 2004). Since HIV is genetically highly variable, escape from T-cell responses by mutations in T-cell epitopes has been put forward as a major reason for the loss of T-cell activity in chronically infected carriers (O'Connor *et al.*, 2001; Peyerl *et al.*, 2004). However, evidence suggests that at least some viral epitopes of HIV are recognized by T cells throughout the chronic phase of infection (Draenert *et al.*, 2004). In addition, levels of virus replication in infected patients were associated in most studies with functional properties of T cells rather than with escape mutations of the virus (Rosenberg *et al.*, 1997; Migueles *et al.*, 2002; Draenert *et al.*, 2004; Hess *et al.*, 2004; Koibuchi *et al.*, 2005). T-cell dysfunctions that have been described in HIV-infected patients or other retroviral infections of animals include impaired antigen-specific T-cell proliferation (Dittmer *et al.*, 1994; Rosenberg *et al.*, 1997, 1999; Lichterfeld *et al.*, 2004), altered cytokine production by CD4⁺ T cells (Clerici & Shearer, 1993), suppressed interferon (IFN) production by T cells (Dittmer *et al.*, 2004) and reduced production of cytotoxic molecules by CD8⁺ T cells (Appay *et al.*, 2000; Migueles *et al.*, 2002; Zelinskyy *et al.*, 2005). However, the mechanisms underlying these features of retrovirus-induced immunosuppression have remained elusive in most of these studies.

One explanation might come from recent studies on regulatory T cells in HIV-infected patients. The generation of regulatory T cells is possibly a normal process that occurs to prevent immunopathological damage (Sakaguchi, 2003). However, immunosuppressive activity by regulatory cells can also lead to the incomplete clearance of a pathogen and subsequently provide conditions favourable for chronic infections (Mills, 2004). Immunosuppressive CD4⁺ T cells, which express the common Treg cell marker CD25, have been described to inhibit HIV-specific T-cell responses (Aandahl *et al.*, 2004; Kinter *et al.*, 2004; Weiss *et al.*, 2004; Andersson *et al.*, 2005). In these studies, the suppression of both CD4⁺ (Aandahl *et al.*, 2004; Kinter *et al.*, 2004; Weiss *et al.*, 2004) and CD8⁺ (Aandahl *et al.*, 2004; Kinter *et al.*, 2004) T-cell functions have been reported. Mainly IFN- γ production by T cells and cell proliferation were affected by Treg cells from HIV-infected patients. The CD25⁺ CD4⁺ Treg cells produced the immunosuppressive cytokines IL-10 and tumour growth factor β (TGF- β), but their suppressive activity was mainly cell-contact dependent (Kinter *et al.*, 2004; Weiss *et al.*, 2004). Treg responded specifically to HIV antigens, indicating the presence of virus-specific cells among the CD4⁺ CD25⁺ T-cell subset (Weiss *et al.*, 2004). However, these studies do not clarify whether induced Treg cells or a subset of natural Treg cells suppressed the HIV-specific T-cell responses. While some reports show an expansion of CD4⁺ CD25⁺ in the blood of HIV-infected patients compared with uninfected controls (Weiss *et al.*, 2004), others claimed that the frequency of Treg cells in HIV-infected individuals is unaltered (Aandahl *et al.*, 2004). However, without detailed knowledge of the specificity, activation status and turnover of these cells, it remains unclear whether an expansion of CD4⁺ CD25⁺ T cells is necessary to enhance Treg-

cell activity *in vivo*. Furthermore, one study reported that strong Treg cell function was correlated with low HIV plasma viraemia in patients (Kinter *et al.*, 2004), whereas the results of Andersson *et al.* (2005) imply that the accumulation of Treg cells in lymphoid tissues was associated with high HIV loads. The latter is supported by Ostrowski *et al.* (2001), who showed that HIV-infected patients with disease progression or active virus replication have increased frequencies of CD4⁺ T cells producing IL-10. It is therefore possible that Treg cells contribute to retrovirus escape and the establishment of chronic infections. One problem in interpreting the results from studies of HIV-infected patients is that only correlative data can be obtained, and this makes it difficult to prove experimentally that Treg cells play an important role in HIV pathogenesis. Thus animal models have to be utilized to investigate the immunosuppressive function of Treg cells in retroviral infections in more detail. In the feline immunodeficiency virus (FIV) model, it has been shown that FIV activates Treg cells which suppress effector T-cell responses (Vahlenkamp *et al.*, 2004). Further studies have been performed in murine retrovirus models because they provide the best opportunities in which to investigate T-cell interactions in a living organism. In particular, the FV mouse model has been used to characterize virus-mediated T-cell dysfunction and Treg-cell activity in retroviral infection.

Retrovirus-induced regulatory T cells mediate immunosuppression in mouse models

The Friend retrovirus mouse model. Using the FV model, it has recently been demonstrated that Treg cells induce immunosuppression and contribute to a form of retrovirus evasion from CTL elimination (Dittmer *et al.*, 2004). Pathogenic FV is a complex of two retroviruses, the Friend murine leukaemia helper virus (F-MuLV) and the spleen focus-forming virus (SFFV). Co-infection of cells by the two viruses allows SFFV to spread by being packaged into F-MuLV-encoded virus particles. FV infection of susceptible adult mice induces polyclonal proliferation of erythroid precursor cells, causing severe splenomegaly. This proliferation is caused by the binding of the SFFV gp55 envelope glycoproteins to the erythropoietin receptors of nucleated erythroid cells (Hoatlin & Kabat, 1995). In susceptible mice, which fail to mount protective immune responses, infection leads to fully malignant erythroleukaemias (Hasenkrug & Chesebro, 1997). In addition to erythroleukaemia, FV induces the suppression of antibody and T-cell responses during acute infection (Ceglowski & Friedman, 1968; Morrison *et al.*, 1987). It was previously demonstrated that the severity of FV-induced splenomegaly and immunosuppression was strongly influenced by the H-2D class I gene region of the MHC (Hasenkrug & Chesebro, 1997). Infection of susceptible strains (H-2D^d) leads to lethal leukaemia, whereas although resistant strains of mice (H-2D^b) may be able to control acute infection, they are nevertheless not able to eliminate the virus completely and thus a chronic infection ensues (also referred to as persistent infection in this review). Recent studies indicate that the inability of cytotoxic T cells to eradicate persistent FV infection is related to effector dysfunction in virus-specific CD8⁺ T cells (Dittmer *et al.*, 2004).

CD8⁺ T-cell dysfunction in chronic FV infection. CD8⁺ dysfunction in chronic FV infection has been proven by the failure of adoptively transferred FV-specific CD8⁺ T cells [from T-cell-receptor (TCR) transgenic mice] to reduce viral loads, despite the activation and proliferation of the CD8⁺ T cells in persistently infected mice. Thus, transferred CD8⁺ T cells recognize their cognate antigen in persistently infected mice but do not respond to it effectively. The functional impairment of those CD8⁺ T cells not infected by the virus directly involves the severely reduced production of IFN- γ and the cytotoxic molecules perforin, granzyme A and granzyme B (Dittmer *et al.*, 2004; Zelinskyy *et al.*, 2005). Interestingly, downregulation of the production of these molecules by CD8⁺ T cells seems to be at the translational rather than the transcriptional level. Consequently, CD8⁺ T cells from chronically infected mice are unable to degranulate and kill FV-labelled target cells *in vivo* (Zelinskyy *et al.*, 2005).

Induced Treg cells in FV infection. Evidence from CD4/CD8 T-cell co-transfer experiments implicates CD4⁺ Treg cells in suppressing the ability of CD8⁺ T cells to produce IFN- γ . The downregulation of IFN- γ expression by CD8⁺ T cells correlates with IL-10 production by the co-transferred CD4⁺ T cells from persistently infected mice. The production of the immunosuppressive cytokine IL-10 by CD4⁺ T cells might be involved in functional impairment of CD8⁺ T cells, since IL-10 is associated with reduced IFN- γ production and immunosuppression in acute FV infection (Dittmer *et al.*, 2002). However, other mechanisms of Treg-cell-mediated suppression have been described, such as CTL-associated antigen 4, TGF- β or the as-yet undefined molecules that require cell-to-cell contact which might also play a role in virus-induced immunosuppression (Mills, 2004). Surface markers of Treg cells have recently been analysed in the FV model. CD25 is a widely used marker for natural Treg cells (Sakaguchi, 2003). However, it was shown previously that a population of CD25⁺ CD4⁺ T cells acquires suppressive activity in chronic FV infection which is not present in cells from naive mice (Dittmer *et al.*, 2004). The experiments demonstrated that CD25⁺ CD4⁺ T cells expand during acute FV infection, but no expansion of this population has been detected during chronic infection as yet (G. Zelinskyy and U. Dittmer, unpublished data). Thus, it might be a qualitative rather than a quantitative difference in the CD25⁺ CD4⁺ population that leads to the appearance of CD25⁺ Treg cells during FV infection. Other than the CD4⁺ CD25⁺ Treg cells, a CD4⁺ CD25⁻ population with suppressive activity was found during chronic FV infection (Dittmer *et al.*, 2004). Glucocorticoid-induced tumour necrosis factor receptor (GITR), which has been associated with Treg-cell functions (Shimizu *et al.*, 2002), is a co-stimulatory molecule and seems to be a functional marker of FV-induced Treg cells (G. Zelinskyy and U. Dittmer, unpublished data). The CD4⁺ GITR⁺ subset increases in numbers at around 2 weeks post-infection, the same phase of infection when CD8⁺ T cells lose their function. Thus, this CD4⁺ T-cell population is associated with suppressive activity during acute FV infection. In addition, it has been reported that the treatment of FV- or LP-BM5 retrovirus- (which induces murine AIDS) infected mice with an antibody against GITR can overcome CD8⁺ T-cell dysfunction and retrovirus-induced immunosuppression (Beilharz *et al.*, 2004; Dittmer *et al.*, 2004; He *et al.*, 2004). The findings indicate that GITR, which has been suggested to block the suppressive function of Treg cells or

to make CD8⁺ T cells refractory to Treg-cell suppression (Shimizu *et al.*, 2002; Stephens *et al.*, 2004), might be a functionally important molecule for induced Treg cells in chronic retroviral infection. Another surface marker that seems to be expressed on retrovirus-induced Treg cells is the α E β 7 integrin CD103, an epithelial cadherin-specific integrin involved in the homing and retention of T cells (Ericsson *et al.*, 2004). Similar to CD4⁺ GITR⁺ T cells, a clear correlation was found between the expansion of CD4⁺ CD103⁺ T cells and the development of CD8⁺ dysfunction during acute FV infection (G. Zelinskyy and U. Dittmer, submitted). Recently, it has been published that CD103 controls the retention of Treg cells at a site of *Leishmania major* infection (Suffia *et al.*, 2005). However, it is not clear why splenic Treg cells from mice persistently infected with FV express CD103, since the spleen does not normally contain epithelial cells. During chronic FV infection, more the 70 % of the CD4⁺ GITR⁺ or CD4⁺ CD103⁺ T-cell populations were also positive for the Treg-cell-specific transcription factor Foxp3 (Sakaguchi, 2005), implying that these cells do indeed perform regulatory functions (G. Zelinskyy and U. Dittmer, submitted). Co-staining experiments for all these different Treg-cell markers have revealed that two main CD4⁺ T-cell subpopulations might be involved in the suppression of CD8⁺ T-cell activity in FV infection, namely the CD25⁺ GITR⁺ CD103⁺ T cells and the CD25⁻ GITR⁺ CD103⁻ T cells. Taken as a whole, these experiments indicate that different populations of induced CD4⁺ regulatory cells play a major role in CD8⁺ T-cell dysfunction during persistent FV infection and thereby contribute to viral persistence. In HIV infection, only the population of CD4⁺ CD25⁺ Treg cells has been investigated so far and has been linked to immunosuppression. It is currently impossible to distinguish whether this T-cell population belongs to either the natural or induced Treg cells. Further Treg-cell markers will have to be analysed in future studies to provide the answer to this question with regards to chronic HIV infection.

There is increasing evidence that Treg cells, which are induced during an ongoing infection, are antigen-specific CD4⁺ T cells (Mills, 2004). Their suppressive effect, however, is not restricted to T cells of the same specificity. CD4⁺ T cells from mice persistently infected with FV suppress CD8⁺ T cell rejection of FV-induced tumours as well as antigenically distinct tumours (Iwashiro *et al.*, 2001), indicating that pathogen-induced Treg cells can mediate a more general immunosuppression. A practical intervention that could block Treg-cell activity and reduce viral loads during chronic viral infections could prove invaluable in treating retrovirus-induced immune dysfunction.

Possible mechanisms of regulatory T-cell induction/expansion during retroviral infection

During an ongoing infection, the differentiation of naive T cells into effector T cells is controlled by APCs. The most potent population of this cell subset is that of the DC. DC induce Th-cell responses by presenting exogenous antigen via MHC class II molecules to naive CD4⁺ T cells. However, before they can efficiently present antigen, they have to mature, and this includes the cell-surface expression of MHC molecules, maturation markers and co-stimulatory molecules as well as the induction of cytokine production. Recent evidence suggests that semi-mature or immature DC induce Treg cells instead of Th cells upon presentation of antigens to

naive T cells (Vlad *et al.*, 2005). These immature DC are characterized by their low expression of co-stimulatory molecules such as CD40, CD80 or CD86 and by an impaired secretion of the cytokine IL-12 (Pollara *et al.*, 2005). Many viruses are able to infect DC and subsequently interfere with the virus-mediated maturation process as well as with DC maturation due to other stimuli, like LPS, IFN- α or CD40L (Pollara *et al.*, 2005). This might represent a so-far unrecognized immune-escape mechanism by which viruses can induce Treg cells and subsequently suppress antiviral immune responses. In HIV it has been suggested that the virus infects DC and alters their functional properties (Steinman *et al.*, 2003). The HIV envelope glycoprotein gp120 has been reported to reduce the capacity of DC to produce IL-12, but this did not interfere with DC differentiation (Fantuzzi *et al.*, 2004). The accessory HIV protein vpr seems to have an even stronger effect on DC. This molecule downmodulates the expression of the co-stimulatory molecules CD40, CD80 and CD86 on DC and interferes with the expression of the DC-maturation marker CD83 (Majumder *et al.*, 2005; Muthumani *et al.*, 2005). In addition, HIV-1 vpr inhibits the production of IL-12 and upregulates the immunosuppressive cytokine IL-10 in DC. Furthermore, DC infected with HIV significantly reduce the activation of specific CTL (Majumder *et al.*, 2005), indicating their immunosuppressive potential. Results from Granelli-Piperno *et al.* (2004) and Krathwohl *et al.* (2006) imply that HIV-infected DC are able to induce Treg cells that can suppress effector T-cell responses. The suppressive effect was partially dependent on IL-10 production by the Treg cells. Similar to HIV, FV productively infects DC and interferes with their maturation. This results in an impaired T-cell activation by FV-infected DC (F. Krux and U. Dittmer, unpublished results). Interestingly, activation of infected DC by immunostimulatory CpG oligodeoxynucleotides *in vivo* is efficient in reducing FV-induced immunosuppression (Kraft *et al.*, 2005). Thus, the infection of DC seems to be a common feature of retroviral infections and is associated with the appearance of induced Treg cells and CTL dysfunction. An alternative mechanism for the induction of Treg cells in viral infections might be a preferential stimulation of Treg cells rather than Th cells by certain antigens of pathogens. This has at least been reported for some bacterial and parasite infections (e.g. *Bordetella pertussis* toxin; Mills, 2004). However, until now no retroviral antigen has been described that preferentially stimulates Treg-cell responses. Although the induction of Treg cells and their suppressive mechanisms have still not been completely understood in retroviral infections, there is increasing evidence that they play an important role in retrovirus-induced immunosuppression which might result in chronicity, a hallmark of retroviral infections. Understanding the cellular and molecular mechanisms of Treg-cell-mediated immunosuppression will certainly open new avenues for the immunotherapeutic treatment of chronic retroviral infections.

Measles virus: the T-cell silencing concept

Induction and/or expansion of regulatory Treg cells by viruses is a highly efficient strategy to prevent activation of effector T cells and this has been elegantly documented in the establishment and maintenance of persistent viral infections (Mills, 2004). In this setting, silencing of effector T cells (which, for reasons of simplicity, will be referred to as 'T cells') is

secondary to the activation of Treg cells, a property shown for only some viruses as yet, although it is likely it will be shared by others. In this part of the review, we will focus on a quite different mode of T-cell silencing, namely that induced directly by viruses and/or their gene products. The outcome of such an interaction, on a cellular basis, could range from cell death by lysis or apoptosis to impairments of signal transduction while, at the level of the organism, T-cell depletion (including that of precursor cells), aberrant homing or malfunction would result in a generalized, antigen-unspecific immunosuppression. In humans, only two viruses are known to induce such a profound suppression of T-cell activation, namely HIV and measles virus (MV), both of which have been studied extensively in this context. This part of the review will focus on principles of T-cell silencing mainly described for MV which, however, not surprisingly, share some similarity to those seen for HIV.

In contrast to retroviral infections dealt with above, MV causes an acute, clinically apparent disease which is contracted only once in an individual's lifetime, usually during childhood. It ranks amongst the most contagious viruses known; transmission is highly efficient and morbidity/mortality rates were high in the prevaccine era and still, in spite of the availability of this efficient vaccine, more than 40 million cases of acute measles are reported annually worldwide with more than 800 000 infant deaths (Clements & Cutts, 1995). As with most, if not all, acute viral infections, measles follows a self-limiting course, with induction of cellular immunity being essential for overcoming the disease. Thus, underlying T-cell deficiencies in patients put them at high risk of severe or even fatal courses of measles. In fact, efficient activation of a virus-specific immune response leading to apparent virus clearance and followed by a long-lasting, if not lifelong, immunity to clinically apparent reinfection are well documented for acute MV wild-type infections (Griffin, 1995). Highly efficient seroconversion and long-lasting protection are also induced by mono- or trivalent (in combination with mumps and rubella) vaccination, particularly when the vaccine is implemented at the recommended two-dose strategy (Broliden *et al.*, 1998). Vaccination is the only efficient means to combat serious sequelae of acute measles. In industrialized countries, these mainly include pneumonia, but also central nervous system (CNS) complications, one of which, subacute sclerosing panencephalitis (SSPE), relies on the only unequivocally documented persistence established by MV in the apparently immunocompetent host (Katz, 1995; Schneider-Schaulies *et al.*, 2003a). This disease, which has been studied as the paradigm for slow virus infections of the CNS, is almost exclusively fatal, yet rare (affecting 1 in 10 000 cases of acute measles) and does not account for the majority of measles-related cases of infant death. Most such deaths follow generalized suppression of immune responses that is induced during and lasts for several weeks after acute measles in developing countries. There, exposure occurs early in infancy, when fading maternal antibodies prevent successful vaccination yet are no longer protective against wild-type MV infection (Black *et al.*, 1986; Lennon & Black, 1986; Ryon *et al.*, 2002; Williams *et al.*, 1995). Further aggravated by malnutrition, secondary infections then often follow a severe or fatal course (Dollimore *et al.*, 1997). Furthermore, persistent infections by other pathogens may be reactivated or exacerbated as a result of MV-induced immunosuppression in children and young adults (Black *et al.*, 1996; Tamashiro *et al.*, 1987). MV was the first

pathogen noted to cause immunosuppression, almost a century ago, when von Pirquet first coined the term 'anergy' to describe immunological impairment in a clinical condition when he described the transient loss of delayed-type hypersensitivity responses to tuberculin during measles. Impairment of T-cell activation *in vivo* is probably reflected *in vitro* by the failure of peripheral blood lymphocytes isolated from patients to expand in response to polyclonal and antigen-specific activation (Griffin & Ward, 1993; Griffin *et al.*, 1989; Ward *et al.*, 1990, 1991). Further hallmarks of immunological abnormalities in measles are a marked lymphopenia and a switch from an initial Th1 to a long-lasting Th2 response (Griffin & Ward, 1993; Griffin *et al.*, 1989; Ward *et al.*, 1991). Since the latter is not likely to result from a direct interaction of viral gene products with the T cell but rather from that with professional APCs, this will not be considered in detail within this review.

Lymphopenia associated with MV

Measles is associated with lymphopenia affecting B cells, monocytes and neutrophils as well as CD4 and CD8 T cells, the extent of which seems to be related to the age-dependent severity of the disease (Okada *et al.*, 2000, 2001). In contrast to B-cell frequencies, which can still be below control levels for up to 6 weeks, numbers of T cells return to normal after 10 days and the CD4/CD8 ratio remains constant over time (Arneborn & Biberfeld, 1983; Okada *et al.*, 2001; Ryon *et al.*, 2002).

Are T-cell precursors affected?

Prohibition of thymocyte generation and viability of or differentiation into T cells can certainly be viewed as an efficient means of affecting T-cell frequencies in the periphery. MV was found to target CD34⁺ human haematopoietic stem cells (HSCs) *in vitro* (Manchester *et al.*, 2002). Though CD150, the entry receptor for all MV strains (Tatsuo *et al.*, 2000; Yanagi *et al.*, 2002), is expressed on and has recently been shown to be characteristic for highly purified fraction of HSCs *ex vivo* (Kiel *et al.*, 2005). MV infection of these cells *in vitro* was possible, yet did not affect their haematopoietic capability. Rather, the ability of MV-infected stroma cells to support HSC development was impaired (Manchester *et al.*, 2002) (Fig. 2). In contrast to the interaction of MV with HSCs, which has only been studied *in vitro* as yet, that with thymocytes has been addressed in various experimental settings. Thymocytes express CD150 (Aversa *et al.*, 1997; Sidorenko & Clark, 2003) and could thus support MV entry and possibly replication. Indeed, expression of MV proteins was detectable in thymocytes (and CD4 and CD8 T cells) of mice in which transgenic expression of CD150 was driven by an Lck promoter after infection *in vivo* or *in vitro* (Hahm *et al.*, 2003). Although likely to occur, thymocyte apoptosis was not analysed in this study. In contrast, massive thymocyte apoptosis was induced by MV in human thymus/liver xenografts in severe combined immunodeficiency (SCID) mice, where thymocytes themselves, however, remained clearly uninfected (Auwaerter *et al.*, 1996; Valsamakis *et al.*, 1999). It is therefore likely that thymocyte viability and/or differentiation into functional T cells is affected not primarily by direct infection but rather by infection of supporting cell types such as thymic epithelial cells, which release viral components (Valentin *et al.*, 1999) (Fig. 2). Since

CD150 ligation by antibodies can provide both activatory and inhibitory signals to lymphocytes (Sidorenko & Clark, 2003), engagement by its viral ligand, the MV haemagglutinin (H) protein, could impact on thymocyte viability as well. Interestingly, prolonged passage of avirulent MV vaccine strains in human thymic tissue enhanced their ability to cause thymocyte apoptosis (Valsamakis *et al.*, 1999). Strikingly, however, thymic output was even increased in measles patients as assessed by TCR rearrangement excision circle (TREC) frequencies directly *ex vivo*, indicating that depletion of T-cell precursors may not contribute to a significant extent to T-cell lymphopenia (Permar *et al.*, 2003) (Fig. 2). Rather, destruction of T cells by viral infection directly or indirectly, for instance by the induction of enhanced sensitivity to apoptosis, appears more likely. Indeed, evidence for the latter phenomenon was provided after CD3-ligation of T cells of patients *ex vivo* (Addae *et al.*, 1995, 1998; Okada *et al.*, 2000) (Fig. 2). Underlying mechanisms have not been identified, but clearly did not involve direct T-cell infection, as the frequency of MV-infected peripheral blood lymphocytes is very low any stage of acute disease (Borrow & Oldstone, 1995; Griffin, 1995). This is apparently in striking contrast to what has been found for the close relatives of MV, rinderpest virus (RPV) or canine distemper virus, where infected T cells were detected at high frequency in cattle or ferrets, respectively (Heaney *et al.*, 2002; von Messling *et al.*, 2004). T-cell depletion could occur, however, in secondary lymphoid tissues by acquisition of MV or apoptotic signals from professional APCs. In support of this hypothesis, fusion or apoptosis was found to be induced in co-cultures with MV-infected DC (Fugier-Vivier *et al.*, 1997; Grosjean *et al.*, 1997; Servet-Delprat *et al.*, 2000; Vidalain *et al.*, 2000, 2001) (Fig. 2). How transmission from DC to T cells occurs and, if so, whether it involves cell fusion is unknown, as unstimulated T cells do not express CD150 (Aversa *et al.*, 1997). MV infection of DC may, however, not even be required for transmission, as the MV F/H glycoprotein complex was recently found to target DC-SIGN on DC and thus, as shown for HIV, MV may also be targeted to a late endosomal compartment from where it could relocate to the cell membrane (Geijtenbeek & van Kooyk, 2003; van Kooyk & Geijtenbeek, 2003). Whether T-cell apoptosis occurs in secondary lymphoid tissues *in vivo*, possibly induced by MV-infected DC, is unknown. Massive apoptosis, as clearly seen in lymphoid tissues of RPV-infected cattle (Stolte *et al.*, 2002), has not been documented after MV infection to date. Giant cell formation and necrosis were reported in lymphoid tissues of MV-infected rhesus macaques, albeit to a moderate extent (Kobune *et al.*, 1996; McChesney *et al.*, 1989; van Binnendijk *et al.*, 1995). Giant cell formation in hyperplastic lymphoid tissue was documented in a measles patient at autopsy; however, MV could not be detected in this area (Nozawa *et al.*, 1994). Thus, although T-cell loss in secondary lymphoid tissues may occur, evidence for that is indirect as yet. What has, however, been measured both in infected children and vaccinees is a preferential decrease in the frequency of LFA-1^{high} T cells, which may indicate that these may home aberrantly to peripheral tissues (Nanan *et al.*, 1999) (Fig. 2). In summary, in acute measles, various mechanisms may account for T-cell depletion. The contribution of T-cell loss to the generalized immunosuppression remains unclear, however, since the duration of the latter clearly exceeds that of lymphopenia.

Viral proteins effective in silencing T cells

The ability of MV to cause cell-cycle arrest in infected cells including T cells is well known. Moreover, MV infection seems to affect lymphocyte effector functions that are not yet established, while those acquired prior to infection are retained (Borrow & Oldstone, 1995; Casali *et al.*, 1984). The vast majority of T cells isolated from patients or experimentally infected animals is uninfected, yet is unable to expand in response to mitogenic signals. Evidently, mechanisms other than direct infection have to be involved and to be provided *in vivo* by a minority of infected cells. As far-reaching effects often relate to the production of inhibitory factors, these have been looked at in measles as well, with only moderate success. Analyses *ex vivo* do not support deficiencies in IL-2 production or a lack of IL-2R expression (Griffin & Ward, 1993; Moss *et al.*, 2002). Elevated levels of IL-10 are not seen consistently (Moss *et al.*, 2002; Okada *et al.*, 2001), and it is still unclear whether type I IFNs are produced at significant levels *in vivo* upon MV infection. In human peripheral blood lymphocyte cultures, vaccine but not wild-type MV strains were potent IFN inducers (Naniche *et al.*, 2000). In contrast, induction of these cytokines by the same wild-type strain was linked to developmental alterations of murine DC transgenic for CD150 (Hahm *et al.*, 2005). This apparent paradox was recently explained by the finding that MV wild-type strains cause type I IFN production in CD150 transgenic murine DC but not in human DC (Shingai *et al.*, 2005). As shown for related viruses, it appears that MV V and/or C proteins modulate the type I IFN response (Ohno *et al.*, 2004; Palosaari *et al.*, 2003; Shaffer *et al.*, 2003), but potential strain-specific differences have not yet been analysed. Evidence obtained *in vitro* suggested the production of a T-cell proliferation-inhibiting factor(s) which has, however, not yet been identified (Fujinami *et al.*, 1998; Sun *et al.*, 1998). IL-10 or type I IFN antibodies did not neutralize the inhibitory effect. In contrast, polyclonal MV-specific antibodies were effective at neutralizing the inability of MV-infected T-cell cultures to proliferate in response to mitogenic stimulation (Sanchez-Lanier *et al.*, 1988; Yanagi *et al.*, 1992), indicating that viral proteins were directly involved.

The N protein

The nucleocapsid (N) protein is the major constituent of both the intracellular and extracellular (enveloped) virion. In addition to complexing the viral RNA genome and the P protein with its core domain, the N protein interacts, via its C terminus, with cellular proteins such as Hsp72 and IRF-3, thereby modulating virus replication and IFN induction, respectively (tenOever *et al.*, 2002; Zhang *et al.*, 2002). As it is a cytoplasmic protein, the finding that soluble N protein can act as a ligand for Fc γ RII on B cells to cause inhibition of antibody production was rather surprising (Ravanel *et al.*, 1997) (Fig. 3). Even more striking, injection of N protein into mice was found to reduce T-cell rather than B-cell responses (Marie *et al.*, 2001). This apparent discrepancy was solved by follow-up studies in mice which revealed that the N protein acts indirectly on T cells by modulating DC functions via interaction with Fc γ RII, thereby preventing IL-12 production and the generation of inflammatory reactions (Marie *et al.*, 2002, 2004). When applied exogenously *in vitro*, recombinant N protein causes calcium influx in thymic epithelial cells and inhibits proliferation of a variety of cell types including activated but not resting human

primary T cells (Laine *et al.*, 2003). While the ability of N protein to induce apoptosis relies on binding of its core domain to the Fc γ RII, the ability to induce G₁ arrest was attributed to the interaction of its C-terminal tail domain with an as-yet unknown receptor (Laine *et al.*, 2003, 2005) (Fig. 3). The C-terminal domain of N protein is, however, highly variable, and is actually therefore used for genotype assignment for MV strains. It would therefore be important to determine whether particularly MV wild-type strain-derived N proteins would inhibit T-cell proliferation via their C termini as efficiently as those of vaccine strains studied to date. MV-infected cells dying from apoptosis and/or secondary necrosis, for instance thymic epithelial cells, are considered as a source of extracellular N protein (Laine *et al.*, 2003, 2005) (Fig. 2). Alternatively, N protein can gain access to late endosomal compartments in infected cells, where it recruits Fc γ RII, and this allows for surface transport (where receptor-bound N protein could act in neighbouring cells) and/or release into the extracellular medium (Marie *et al.*, 2004). Whether there is a role of N protein for T-cell silencing *in vivo* remains questionable. Firstly, the putative cell-surface ligand that combines N protein is only found on T cells that are already activated (Laine *et al.*, 2003), which would confine inhibitory signals to this particular population. Secondly, a recombinant MV which expressed vsV G protein instead of the authentic MV F/H glycoprotein complex failed to induce T-cell arrest *in vitro* and *in vivo* (see below), indicating that N protein may not be essential, at least for T-cell silencing.

Signalling by viral glycoproteins

Evidence for the ability of the MV glycoprotein complex, consisting of the haemagglutinin (H) and the proteolytically activated F_{1/2} heterodimer, to signal to T cells came from a number of experiments *in vitro* and *in vivo*. *In vitro*, MV virions, but not those derived from a recombinant expressing vsV G protein on their surface, prevented expansion of T-cell lines and that of mitogen- or CD3/CD28-driven primary human or rodent T cells in a dose- and contact-dependent, but infection-independent, manner. The inhibitory activity of the viral glycoprotein complex was confirmed in experiments where co-culture with cell lines transfected to co-express F and H protein (both not with those expressing F or H protein alone) caused T-cell arrest *in vitro*. Importantly, transfer of these doubly transgenic cells into cotton rats significantly impaired the ability of T cells isolated from these animals to expand in response to mitogenic stimulation (Avota *et al.*, 2001; Niewiesk *et al.*, 1997, 1999; Schlender *et al.*, 1996; Schnorr *et al.*, 1997; Weidmann *et al.*, 2000a). The requirement for the F/H glycoprotein complex as effector structure for T-cell inhibition was confirmed for related viruses such as RPV and peste-de-petits-ruminants virus (PPRV) (Heaney *et al.*, 2002). While proteolytic processing of the F protein is required for contact-mediated T-cell arrest, the fusogenic activity of the glycoprotein hetero-oligomeric complex is not (Weidmann *et al.*, 2000a, b). Since the inhibitory activity of the F₀/H complex is restored after exogenous trypsin treatment and thereby F protein cleavage, the actual effector domain most likely resides within the F protein and is conformational. The H protein may strengthen the interaction of the complex with the target cell surface by binding to its receptor(s) (see below) or act as a chaperone to stabilize the conformation of the F_{1/2} protein. Interestingly, the F protein of respiratory syncytial virus (RSV) can also inhibit T-cell proliferation

in vitro (Schlender *et al.*, 2002). T-cell silencing induced by viral glycoproteins did not involve induction of apoptosis or interfere with stimulated upregulation of surface markers (including the IL-2R α -chain) or cytokine release, but rather prevented entry of these cells into S phase (Avota *et al.*, 2001; Engelking *et al.*, 1999; Niewiesk *et al.*, 1999; Schneider-Schaulies & ter Meulen, 2002; Schnorr *et al.*, 1997).

The receptor(s)

Although, at least for MV, contact-dependent T-cell arrest requires co-expression of the H protein, this arrest does not depend on the known MV entry receptors (Fig. 3). Firstly, MV F/H proteins effectively arrest proliferation of murine T cells, which do not express either of the two known H-protein-binding receptors, CD46 and CD150 (Dorig *et al.*, 1993; Erlenhöfer *et al.*, 2002; Nanche *et al.*, 1993; Tatsuo *et al.*, 2000). Secondly, CD46- or CD150-specific antibodies do not prevent silencing of human T cells (Erlenhoefer *et al.*, 2001). Thirdly, both molecules were found to promote rather than inhibit TCR signalling (Astier *et al.*, 2000; Sidorenko & Clark, 2003; Zaffran *et al.*, 2001). Various effects of CD46 ligation by its natural ligands (complement components C3b/C4b), antibodies and, importantly, MV H protein on APCs or T cells have been described in molecular and functional terms; these include enhanced vulnerability to complement-mediated lysis (due to receptor downregulation) (Schneider-Schaulies *et al.*, 1996; Schnorr *et al.*, 1995) and modulation of inflammatory cytokine production (Marie *et al.*, 2001, 2002) or potential interference with TLR signalling and thereby inhibition of IL-12 production (Karp *et al.*, 1996) (Fig. 3). However, since high-affinity interaction with CD46 is a property of attenuated and not of wild-type MV strains (Hsu *et al.*, 2001; Ono *et al.*, 2001; Yanagi *et al.*, 2002), the relevance of these findings for immunosuppression *in vivo* remains to be determined. For this, CD150 would be expected to be more important, not least because its expression is crucial for cell and tissue targeting of wild-type MV and other morbilliviruses (Erlenhöfer *et al.*, 2002; Hahm *et al.*, 2003; Minagawa *et al.*, 2001; Ohgimoto *et al.*, 2001; Schneider *et al.*, 2002; Tatsuo & Yanagi, 2002). Within the T-cell compartment, CD150 expression is confined to activated cells (Aversa *et al.*, 1997) and this, together with the co-stimulatory properties of the molecule, argues against the direct role of CD150 in contact-dependent T-cell silencing. Moreover, CD150 certainly does not interact with morbillivirus F proteins which are likely to harbour the effector domains (see above). Cell-surface molecules interacting with RSV or morbilliviruses include TLR2 and TLR4 (Bieback *et al.*, 2002; Kurt-Jones *et al.*, 2000), DC-SIGN (de Witte *et al.*, 2006) (Fig. 3) and substance P receptor (Harrowe *et al.*, 1990, 1992). However, these are either not expressed on human T cells (such as the TLRs and DC-SIGN) or not further analysed in terms of their ligands (substance P receptors). Moesin has also been shown to enhance MV uptake (Dunster *et al.*, 1995; Schneider-Schaulies *et al.*, 1995), although it does not appear to act by direct binding of MV. Thus, moesin may have an indirect role in reorganization of the actin cytoskeleton once MV has interacted with the cell surface, and this could be important for viral uptake and also for clustering of signalling receptors or T-cell plasticity.

The signal

Consistent with the observation that the release of cytokines is largely unaffected, MV contact does not affect the IL-2R-dependent activation of the JAK/STAT pathway in T cells. In contrast, activation of the phosphatidylinositol 3-kinase (PI3K)/Akt kinase pathway after IL-2R or CD3/CD28 ligation was efficiently blocked shortly after MV exposure *in vivo* and *in vitro*, while interference with activation of MAPK required longer MV exposure (Avota *et al.*, 2001, 2004) (Fig. 4). MV is so far the only pathogen shown to interfere with activation of this particular pathway; given its important role in conveying survival and mitogenic if not oncogenic signals, some viruses activate this particular pathway (Cacciotti *et al.*, 2005; Dawson *et al.*, 2003; Yu & Alwine, 2002; Yuan *et al.*, 2002). Downstream effectors of this kinase include subunits of cyclin-dependent kinases essentially involved in S-phase entry and, consequently, these were found to be deregulated in T-cell cultures exposed to or infected with MV (Engelking *et al.*, 1999; Nanche *et al.*, 1999). The importance of interruption of Akt kinase activation for MV-induced T-cell silencing was documented directly, as transgenic expression of a catalytically membrane-targeted active Akt kinase largely abolished the inhibitory signal (Avota *et al.*, 2001). The regulatory subunit of the PI3K, p85, which acts upstream of Akt kinase activation, was tyrosine-phosphorylated shortly after TCR ligation in MV-exposed T cells, yet failed to redistribute to cholesterol-rich membrane microdomains (also referred to as lipid rafts), and this correlated with a lack of TCR-stimulated degradation of Cbl-b protein (Avota *et al.*, 2004). Importantly, MV can bind and cluster lipid rafts on the T-cell surface, indicating that signalling by the F/H protein complex is probably initiated by interaction of MV with molecules within these membrane domains (Fig. 4). Most likely as a consequence of its ability to block PI3K activation, MV signalling interferes with activation of the guanosine exchange factor Vav, and this would be expected to affect cytoskeletal rearrangement occurring in response to TCR activation as well.

Does T-cell silencing exclude a contribution of silencing T cells in measles pathogenesis?

Although we have focused in the second part of this review on a direct role of viral constituents in regulating T-cell generation, differentiation, survival or activation, this in no way excludes the possibility that APCs also play an important role in MV-induced immunosuppression. As a prerequisite, MV should be able to target APCs and modify their viability, differentiation and function in a way that would allow for expansion or induction of Treg cells. While monocyte/macrophages have been identified as MV target cells in humans (Esolen *et al.*, 1993), infection of DC has not been documented. A very limited number of splenic DC isolated from mice transgenic for CD150 was MV-positive in one study (Hahm *et al.*, 2004), while detection of infected CD11c⁺ cells was only achieved after additional ablation of the type I IFN system or after depletion of macrophages (Mrkic *et al.*, 2000; Shingai *et al.*, 2005). The relevance of these findings is unclear, however. In the first study, CD150 expression was driven by the CD11c promoter so that DC were the only cells that could be targeted by MV (Hahm *et al.*, 2004, 2005). The second approach seems to confirm that the IFN system is an important factor in species restriction of MV; however, it may not be switched on by wild-type MV in

human DC (Shingai *et al.*, 2005). Lastly, in YAC-CD46 transgenic mice (which were also IFNR knockouts), infection of DC required depletion of monocyte/macrophages, indicating that these rather than DC are the main targets (Mrkic *et al.*, 2000). In the two animal models that allow efficient MV infection by the natural intranasal route, namely rhesus macaques and cotton rats, DC infection has not yet been studied. Interestingly, however, the expression of wild-type MV-derived H proteins conferred tropism of recombinant MV for DC *in vitro* and for secondary lymphoid tissues *in vivo* (Niewiesk *et al.*, 1999; Ohgimoto *et al.*, 2001; Pfeuffer *et al.*, 2003). If the latter *in vivo* tropism would reflect MV targeting to DC, this would parallel observations made for lymphocytic choriomeningitis virus, where exchange of a single amino acid within the glycoprotein conferred DC tropism and immunosuppressive activity (Sevilla *et al.*, 2000, 2003, 2004). The induction of a highly efficient virus-specific immune response implies that DC are able to acquire and present MV at least at early stages after exposure. Whether they are able to support a full MV replication cycle *in vivo*, as they do *in vitro*, or whether priming of T-cell responses involves crosspriming or processing of viral structures after endocytosis is unknown. Evidence obtained *in vitro* suggests that MV infection leads to DC depletion by fusion and apoptosis (Fugier-Vivier *et al.*, 1997; Servet-Delprat *et al.*, 2000), while a recent study suggests that, again *in vitro*, MV-induced type I IFN would impair differentiation of DC from their precursors (Hahm *et al.*, 2005). Whether this also occurs in a natural infection has not been documented. As indicated above, it is not clear whether and by which cell types type I IFN is induced by wild-type MV infection and, if so, whether the levels required for inhibition of DC development are ever reached, be it locally or systemically. If infection of DC does occur *in vivo*, how could they contribute to T-cell silencing? If contact-dependent signalling to T cells was a major mechanism of immunosuppression, it would certainly be attractive if the glycoprotein complex were to be expressed on the surface of DC efficiently, since these are permanently scanned. In addition, however, these cells do polarize the T-cell response, and it is considered another hallmark of MV-induced immunosuppression that Th1 responses are replaced rapidly by a long-lasting predominant Th2 profile. Are there scenarios in MV pathogenesis where Treg cells could be expanded or induced? This has not yet been addressed directly, but incomplete or aberrant maturation and production of type I IFN and IL-10 rather than IL-12 (reviewed by Schneider-Schaulies *et al.*, 2003b) as seen in infected DC could provide a favourable environment. Moreover, co-ligation of CD3 and CD46 by antibodies on T cells can drive differentiation of Tr1 cells *in vitro* (Kemper *et al.*, 2003, 2005). A similar scenario could be envisaged with DC expressing MV H protein, although this would be limited to CD46-interacting MV strains. As Treg cells can control persistent infections, they may also have a role in the establishment and/or maintenance of the persistent MV CNS infection SSPE, where no deficiencies of effector T-cell functions have yet been found. Lastly, MV can trigger post-infectious encephalitis, which is generally believed to represent virus-induced autoimmune disease (Johnson *et al.*, 1983), and Treg cells might also have a role to play there.

Summary: is there a unifying concept of virus-induced immunosuppression?

Silencing T cells and T-cell silencing are, as summarized in this review, potential strategies employed by viruses to evade ultimate control by the adaptive immune response in order to spread (for MV) and/or to establish and maintain chronic infections (for retroviruses). As outlined above, the two strategies are not mutually exclusive for the viral systems described, as retroviruses doubtlessly also encode proteins that interfere directly with activation of T cells (such as HIV gp120, vpr or nef) and MV has the ability to interfere with APC maturation and thereby might favour the induction and expansion of silencing T cells. The relative importance of the two strategies for individual viral infections may be linked directly to the nature of the infection process. In acute, self-limiting infections where viral proteins are produced in large amounts, the T-cell silencing strategy may prevail, as it may be easier to make proteins to dampen APC and T-cell activation rapidly rather than relying on a time-consuming induction of a regulatory T-cell population that needs to be activated and expanded. Viruses setting up chronic infections have to ensure that clearance during acute infection is not complete, and this may be achieved by viral proteins, but also by the expansion of natural Treg cells which downmodulate functions of effector T cells. This may help to ensure the maintenance of immune escape during chronic infection, when virus replication is usually low and the amounts of viral proteins are therefore limited.

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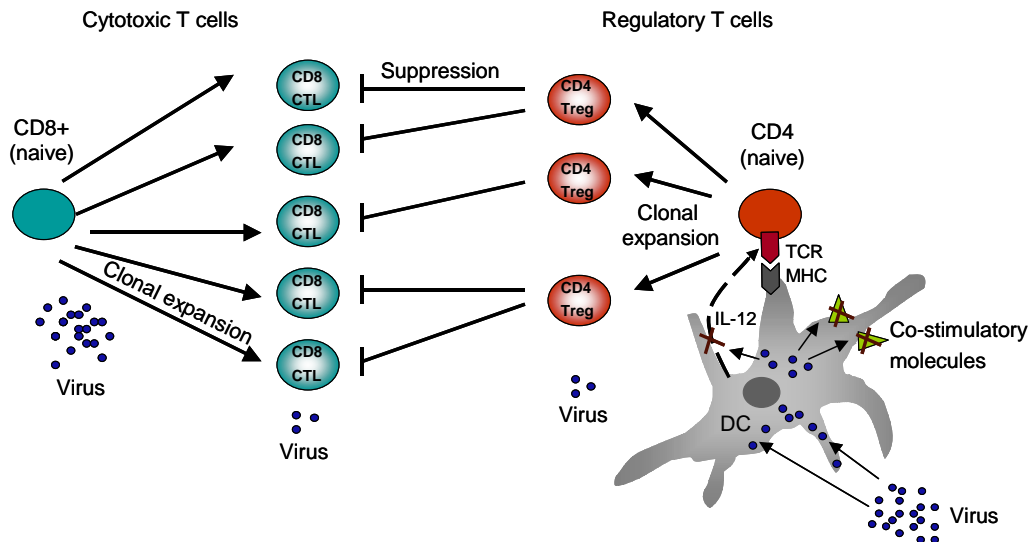


Fig. 1. How induced Treg cells function during a virus infection. When a viral infection occurs, the CD8⁺ CTLs become highly activated and start to proliferate. These cells kill virus-infected cells and thus fight the virus itself. However, once most of the virus has been eliminated, the CTLs have to be suppressed otherwise there is the danger that they may start to attack uninfected cells of the body, thus causing autoimmune disease. This suppression of the CTLs is carried out by CD4⁺ Treg cells. The latter also start to proliferate during the infection, although there is a time delay so that they are only able to start switching off the CTLs once the defence against the virus has been successfully completed. Viruses might disturb this balance between the CTLs and Treg cells by infecting DC and thus interfere with DC maturation and cytokine production. There is experimental evidence that immature DC stimulate Treg cells rather than Th cells, which could result in severe suppression of CTL responses and the development of chronic infections.

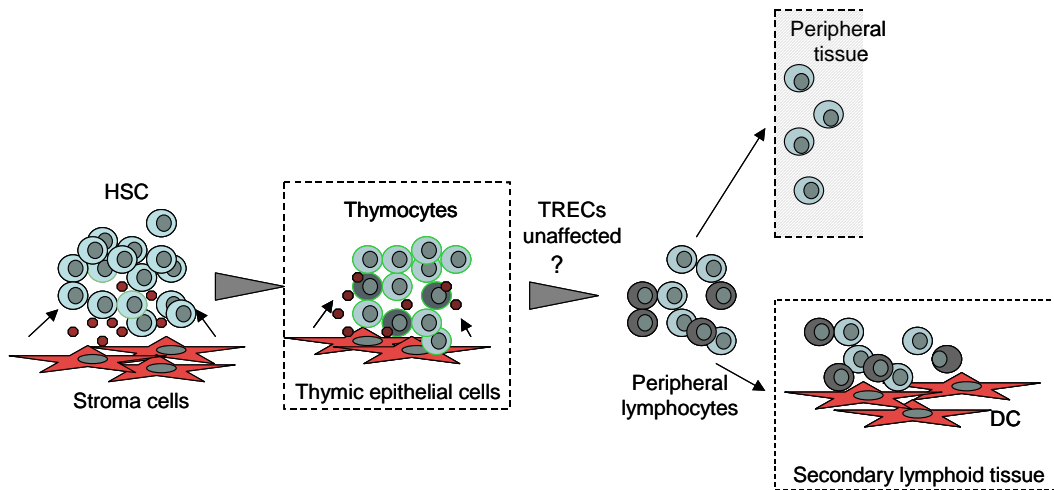


Fig. 2. Potential mechanisms of MV-induced lymphopenia. Only a few HSC express CD150, to low levels (indicated as light-green membrane), yet are not grossly affected by infection. Unknown components released from infected stroma cells (shown in red) interfere, however, with HSC differentiation and this may reduce the number of thymocytes. These express high levels of CD150 (bright-green membrane) and could be depleted by apoptosis, which again is independent of their infection but rather induced by viral components (N protein?) released from infected thymic epithelial cells (in red). Peripheral blood lymphocytes may undergo spontaneous apoptosis or reveal enhanced sensitivity to apoptosis upon stimulation, including that provided by MV-infected DC (shown in red) in secondary lymphoid tissues, or are depleted from the peripheral blood compartment by aberrant homing to tissues.

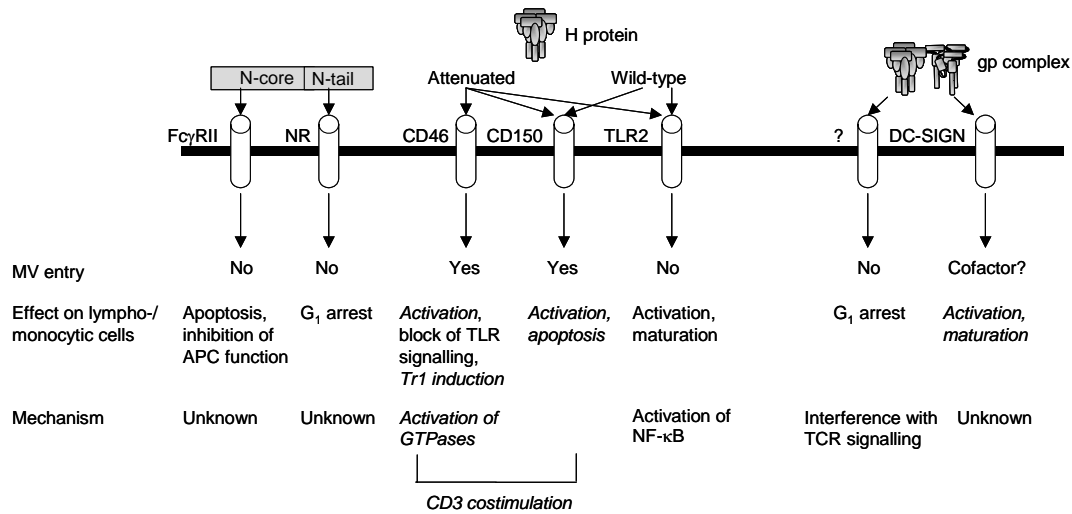


Fig. 3. Ligation of cellular receptors involved in MV interaction: mechanisms and consequences for lymphocyte/monocyte function. Physical and/or functional interaction of MV with cellular surface molecules [CD46 and an unknown N-protein receptor (NR) interacting with the tail domain of the N protein] or those expressed exclusively on haematopoietic cells [Fc γ RII (interacting with the core domain of the N protein), CD150, TLR2, DC-SIGN and an unknown glycoprotein (gp) receptor (?)] also results in or helps entry into target cells or impacts on cellular functions/viability. Consequences of receptor ligation by antibodies that have not been proven to occur after MV binding are indicated in italics.

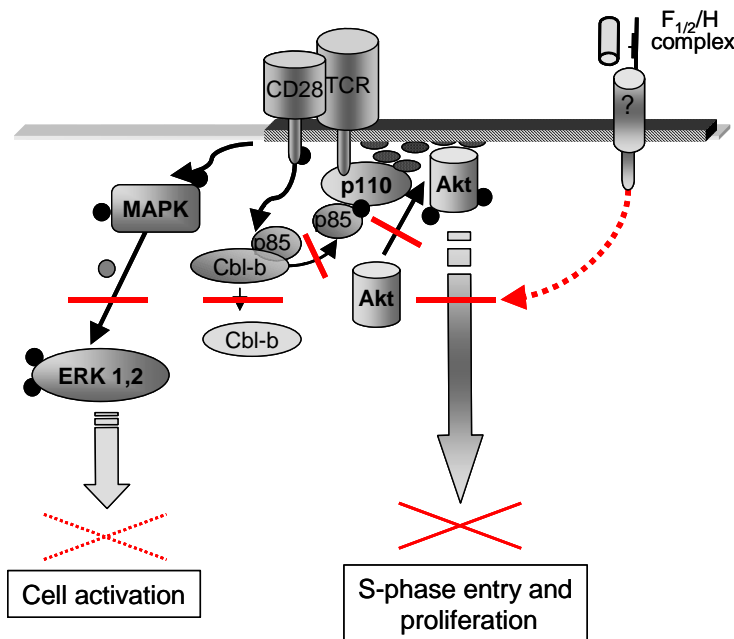


Fig. 4. Interference of MV glycoproteins with activation of TCR/CD28-associated signalling pathways. As a result of TCR ligation and costimulation, signalling pathways are activated that include the mitogen-associated protein kinases (MAPK) and, downstream, extracellular signal-related kinases 1 and 2 (ERK1, 2), and this is prevented 24 h after MV exposure of the cell (indicated by the F_{1/2}/H complex interacting with an unknown receptor, ?; phosphate residues are indicated). This inhibition may partially inhibit cell activation (indicated as dashed cross). Early after exposure, MV signalling interferes with TCR/CD28-dependent degradation of Cbl-b, which is required for the release of p85 for tyrosine phosphorylation, membrane recruitment and complex formation with p110 to form the active PI3K holoenzyme. As a result, of this inhibition, phosphoinositol polyphosphates are inadequately generated and, thereby, membrane recruitment and activation of the Akt kinase are essentially abolished, as is general activation of T-cell signalling from lipid rafts (indicated as dark area in the membrane) required for S phase entry and proliferation.