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Review

Generalized immunosuppression: how viruses undermine the immune response

D. Naniche* and M. B. A. Oldstone

Division of Virology, Department of Neuropharmacology, Scripps Research Institute, IMM6, 10466 North Torrey Pines Rd., La Jolla (California 92037, USA), Fax + 1 858 784 9981, e-mail: naniche@scripps.edu

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Abstract. Following infection, a virus must battle against the host's immune response. Viruses have developed many ways to escape immune surveillance and downregulate the host's immune response. Some viruses cause a generalized immunosuppression, thereby inhibiting or depressing the immune response towards themselves as well as towards unrelated pathogens. This review will focus on the mechanisms involved in the three main human viral infections causing immunosuppression: measles, human immunodeficiency virus and cytomegalovirus. We will also discuss what has been learned from the extensively studied mouse models of viral-induced immunosuppression: lymphocytic choriomeningitis virus and Rauscher leukemia virus. All of these viruses that induce generalized immunosuppression appear to do so by very similar mechanisms. They hinder antigen presentation to T cells and/or hematopoiesis. We will highlight the similarities in the viral targets as well as present evidence for alternate mechanisms.

Key words. Immunology; immunosuppression; virus; infection.

Introduction

Following infection, a virus must battle against the host's immune response. Viruses have developed many ways to escape immune surveillance, and some viruses even use the immune response to their advantage. Viruses that cause persistent infections are obliged to subvert the immune system in order to prevent being recognized and eliminated by the host's immune response. Acute viral infections, on the other hand, may slow or temporarily hamper the immune response in order to maximize their replication and transmission, but they are either eliminated by the host or they eliminate the host. Most viral interference with the immune response is termed either immune evasion or immunosuppression. Viral immune evasion, which can occur by a number of mechanisms, prevents an effective immune response to the initiating virus and is generally of benefit to the virus. Generalized immunosuppression, however, inhibits or depresses the immune response towards itself as well as towards unrelated pathogens. Examples of viral immune evasion include mechanisms such as latency, downregulation of immune regulatory proteins and viral mimicry of host immune regulatory proteins. These mechanisms are extensively reviewed elsewhere and will not be discussed further here. The main mechanisms thought to be involved in virus-induced immunosuppression include destruction of antigen presenting cells (APCs), T lymphocytes or bone marrow progenitor cells and dysregulation of cyokine production.

This review will focus on the mechanisms involved in the three main human viral infections causing immunosuppression: measles, human immunodeficiency virus

* Corresponding author.

(HIV), and cytomegalovirus (CMV). These viruses induce similar states of immune nonresponsiveness, with measles virus being a unique example of a nonpersistent, immunosuppression-inducing infection. We will also discuss what has been learned from the extensively studied mouse models of viral-induced immunosuppression: lymphocytic choriomeningitis virus (LCMV) and Rauscher leukemia virus (RLV).

Viruses exploit common immunological targets

The viruses inducing generalized immunosuppression appear to do so by very similar mechanisms. They hinder antigen presentation to T cells and/or hematopoiesis. In order to discuss the specific pathways involved, we will first give an introduction to these immunological targets of virus-induced immunosuppression.

Specialized APCs called dendritic cells (DCs) are thought to trigger the entire immune response. DCs exist as different subtypes and reside in virtually all tissues. They phagocytose foreign antigens, and upon activation migrate to secondary lymphoid organs such as the spleen and draining lymph nodes where they can stimulate T cells specific for a particular antigen. These activated DCs and another type of APC, the macrophage, then produce the cytokines interferon-α/β type I (IFN-α/β) and interleukin-12 (IL-12) which orchestrate a cascade of reactions that contribute to the generation of an antiviral T-cell response. These early events of T-cell activation determine whether a type 1 (Th1) or type 2 (Th2) effector T cell will be generated. The classification into type 1 and type 2 effectors is based on the observed differential ability of T cells to secrete certain cytokines. The Th1 cytokines, represented by IFN-γ and IL-2, are thought to favor vigorous cytotoxic T cell responses. The Th2 cytokines, IL-4, IL-5 and IL-10 are thought to dampen cellular immunity and favor the antibody response (fig. 1). The importance of DCs in triggering an antiviral immune response has been clearly demonstrated, whereas the initial role of macrophages is unclear.

Hematopoiesis, which gives rise to most of the effector cells of the immune system, also represents a target for

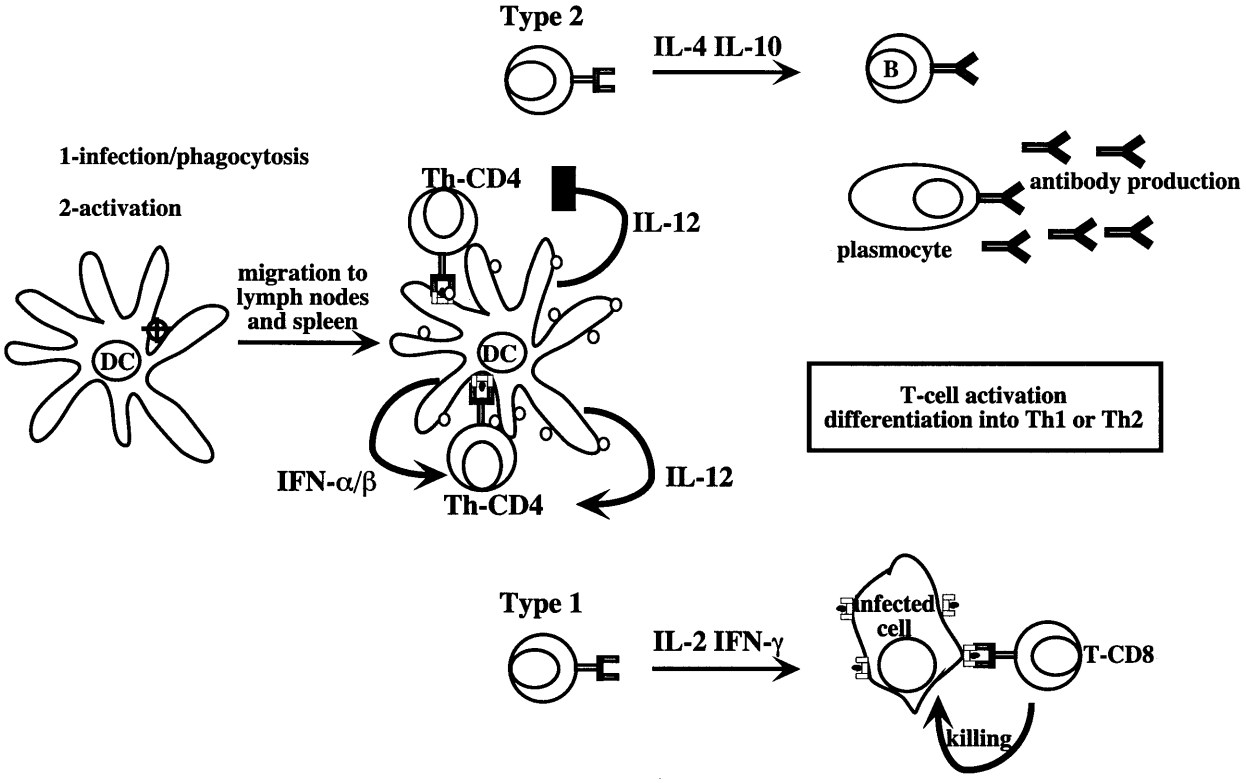

Figure 1. Schematic diagram of the events taking place after dendritic cell (DC) activation. The DC migrates to lymph nodes where it secretes large quantities of IFNα/β and IL-12, thus driving the immune response towards a type 1 cellular response. A type 1 response will lead to T-helper-cell (Th) secretion of IL-2 and IFN-γ as well as cytotoxic T cell activity. A lack of IL-12 and IFNα/β may cause a type 2 response to be favored. This leads to secretion of IL-4 and IL-10 and to a strong humoral antibody response. IL-4 and IL-10 will have an inhibitory effect on type 1 cytokine secretion.

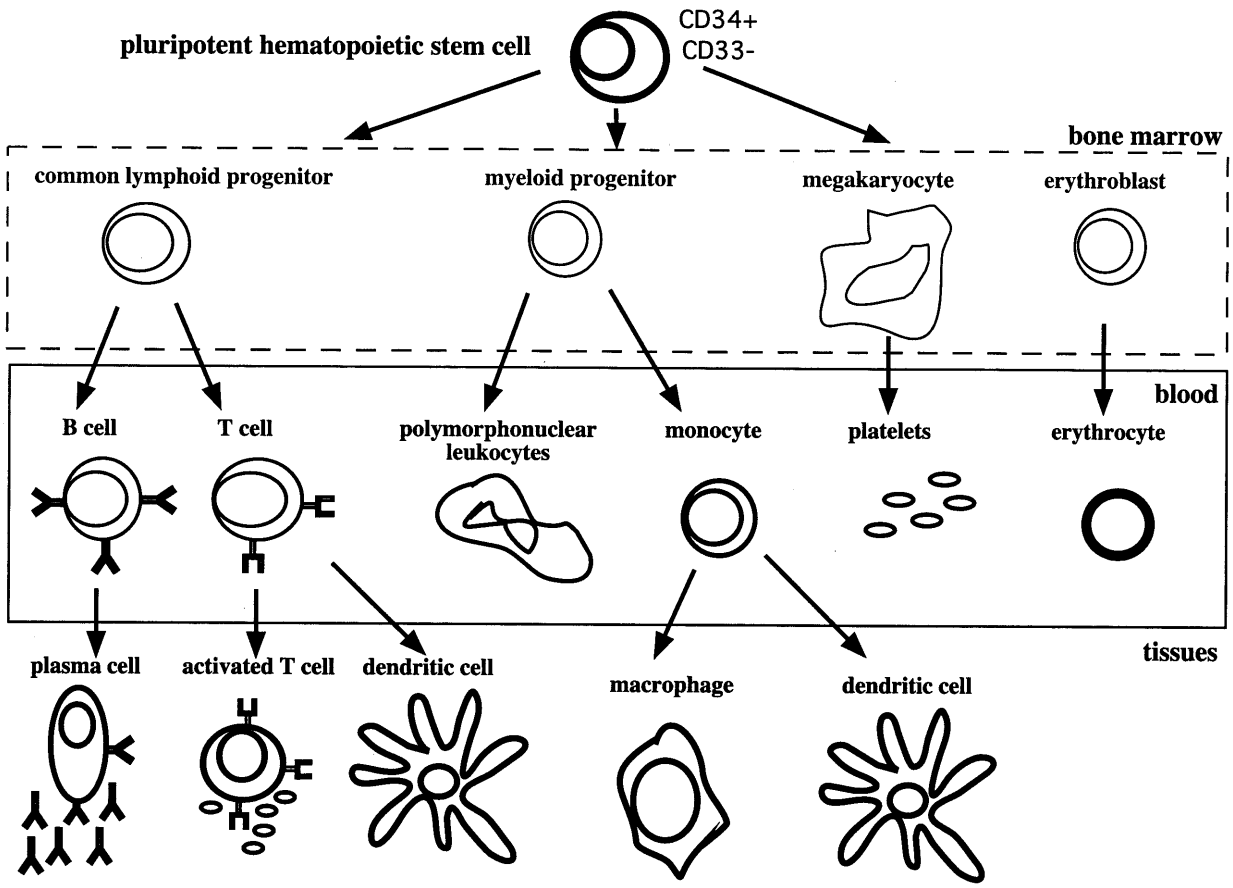

Figure 2. Schematic diagram of hematopoiesis starting in the bone marrow and giving rise to differentiated cells in the blood and tissues. The pluripotent hematopoietic stem cell gives rise to the progenitors, which differentiate into a number of cells including, among others, the immunologically relevant plasma cell, activated T cells, dendritic cells and macrophages. The CD34 and CD33 markers are used to distinguish the early progenitors.

immunosuppressive viruses. The primitive pluripotent stem cells of the bone marrow divide to produce committed progenitor cells of the lymphoid, myeloid, megakaryocyte and erythroid lineages (fig. 2). The earliest progenitors are identifiable by the expression of CD34 surface markers. T and B lymphocytes derive from the lymphoid progenitor cells, whereas macrophages originate from the myeloid progenitors. DCs descend from both the myeloid and lymphoid lineages. Viruses that infect bone marrow cells can selectively disrupt particular hematopoietic lineages by targeting specific differentiation states of the progenitor cells.

Murine models of immunosuppression

LCMV and RLV

The LCMV and RLV animal models were the first to suggest DC dysfunction or destruction as a mechanism of immunosuppression. LCMV, a natural pathogen of mice, is a member of the Old World arenavirus family, which includes the human Lassa fever virus. This model has been important for the elucidation of mechanisms of viral immunosuppression which have proven relevant to human infections such as HIV. A variant of LCMV, clone 13, causes persistent infection accompanied by a generalized immunosuppression in the adult mouse [1]. Mice persistently infected with LCMV clone 13 are unable to mount effective immune responses to other viruses [2, 3] or to parasites [4]. This model first showed that although LCMV clone 13 could elicit a cytotoxic T lymphocyte response, it was not effective and failed to immediately clear the virus. Initial infection by both the immunosuppressive clone 13 and the nonimmunosuppressive parental virus Armstrong occurs in the marginal zone of the spleen. However, as infection progresses, the DCs of the splenic white pulp become preferential targets of the immunosuppressive variants.

The DCs are subsequently destroyed by a CD8 lymphocyte-dependent mechanism [5]. The destruction of these professional APCs thus prevents initiation of an immune response to other pathogens. During acute LCMV infection, the bone marrow is also infected, and this can lead to reduction in the differentiation capacity of the progenitor cells [6]. Whether this dysfunction also occurs during persistent LCMV clone 13 infection is not known. LCMV clone 13 infection does not result in lifelong persistence, and the duration of the persistent infection varies according to mouse strain. A low-level immune response does progress and eventually clears the virus. It is likely that during the persistent phase, LCMV infection leads to destruction of splenic DCs and newly differentiated DCs as they are regenerated from bone marrow. It is not known whether one or more subtypes of DCs are affected. When virus is cleared, the immune response to other pathogens is restored. The return of the immune response to a normal state after disappearance of the virus argues for a peripheral effect on APC generation rather than a more profound effect of LCMV on hematopoiesis.

Similarly to the LCMV model, the murine model of RLV infection has shown that disruption of DCs underlies immunosuppression. RLV is a retrovirus that causes acute pathological effects and tumors which are rapidly lethal. RLV infection is accompanied by immunosuppression with impaired T lymphocyte stimulation [7]. RLV infects peripheral DCs in vivo, and in addition to downregulating their expression of adhesion molecules, RLV infection reduces the ability of peripheral DCs, stimulated with a contact sensitizer, to migrate from their resident tissue to lymph nodes [8]. RLV can also infect DC progenitors in the bone marrow, although it is not known at which stage of differentiation they are infected. Bone-marrow-derived DCs from RLV-infected mice are inhibited in their ability to produce IL-12 and thus to stimulate T cells. However, administration of IL-12 at the time of infection restores the ability of bone marrow DCs to stimulate allogeneic T cells [9]. IL-12 administration also reverses the RLV-induced defect in peripheral DC migration [10]. Although only 20% of the bone-marrow-derived DCs from RLV-infected mice are infected, a slight imbalance of IL-12 production may engender a cycle of decreased DC generation and function.

Both of these murine models have illustrated the importance of IL-12 and/or DCs in triggering an effective antiviral cellular immune response, as well as demonstrating how they can be disrupted: LCMV by destroying DCs and RLV by preventing their migration and inhibiting IL-12 synthesis.

Immunodeficiency-inducing virus infections in humans

Measles: A nonpersistent virus infection inducing a transient immunosuppression

Measles virus (MV) infection has been recognized to be immunosuppressive since the beginning of the 20th century when Clement von Pirquet made the observation that the tuberculin skin test response of immune individuals was transiently inhibited during acute measles [11]. This phenomenon was further documented and shown to include other cellular responses to recall antigens such as vaccinia, diphtheria toxin and *Candida albicans* [12–14]. This transient immunosuppression can last up to 6 months after acute measles infection, and although vaccination with the attenuated virus vaccine also induces immunosuppression, it is much shorter [14–16].

The immunosuppression accompanying measles virus infection has frequently been associated with high morbidity and mortality. In countries where vaccination coverage is high, measles infection and its complications are well controlled. However, in developing countries where vaccination coverage is low, pulmonary complications and opportunistic infections still cause 1–2 million deaths every year.

Mechanisms underlying measles-induced immunosuppression have been suggested and can possibly explain the depressed immune response during acute measles. However, measles presents the interesting and unique case of inducing a prolonged immunosuppression present for months following the infection when there is no detectable virus present. Whether there is indeed an undetected persistent reservoir of that virus maintains suppression during this period or whether the long-lived effect results from acute infection remains to be elucidated.

The nonresponsiveness of measles-infected lymphocytes to mitogenic or antigenic stimulation in vitro has been shown to be due to a G0-like block in the cell cycle that occurs in the presence of partial activation of the lymphocytes [17–19]. It would seem, therefore, that lymphocytes which have been infected by MV cannot become fully stimulated by APCs. In addition to perturbed lymphocyte function, APC function itself has recently been shown to be depressed in vitro. MV infection of DCs not only abolishes their ability to present antigen to T cells but also promotes cell death of T lymphocytes by apoptosis [20–22]. MV-infected cells can also arrest the proliferation of uninfected cells by direct contact [23]. This is thought to be mediated by the properly cleaved MV fusion protein expressed on the surface of infected cells [24].

MV-infected DCs and monocytes, similarly to RLV-infected murine DCs, are impaired in their ability to produce the cytokine IL-12 [21, 25]. Whether the IL-12

deficiency is due to direct infection or to a signal transduced by MV binding to its cellular receptor is not known. Virulent strains of MV also have the ability to inhibit IFN-α/β production in vitro [26]. By inhibiting both IL-12 and IFN-α/β, MV may have established redundant mechanisms to slow the development of the immune response and thus increase its spread and pathogenesis. However, in vivo observations in humans suggest that if there is an IL-12 and/or IFN-α/β deficiency, it does not affect early production of type 1 cytokines, as IFN-γ and IL-2 production are normal at the onset of the cellular immune response and rash [27]. However, as measles progresses, the levels of these type 1 cytokines decrease and give way to a rise in IL-4 levels that is sustained for several months [28]. Since the type 2 IL-4 cytokine is associated with a T cell response favoring humoral immunity, and the type 1 IL-2 and IFN-γ cytokines are associated with cellular immunity, predominance of a type 2 response has been suggested to contribute to immunosuppression in measles patients. Specific subtypes of DCs and/or the way in which these DCs are activated have been shown to influence the type of response elicited from a T lymphocyte. For example, DCs of lymphoid origin have been shown to promote type 1 responses, whereas DCs of myeloid origin are thought to favor type 2 cytokine production [29]. Measles infection may preferentially kill or activate certain subtypes of DCs and dampen the type 1 response while skewing the response to favor type 2.

The duration of measles-induced immunosuppression is variable and depends on the severity of the disease. The mechanisms outlined above are all plausible to explain impaired immune function lasting a few weeks after acute infection, but they are difficult to reconcile with the nature of a longer-lived immunosuppression. The kinetics of DC turnover would be consistent with an immunosuppression lasting up to 1 month. It has been shown in mice that, depending on the location in the organism, DC turnover is achieved in 6 days for airway epithelium DCs, or in up to 30 days for skin Langerhans DCs [30]. In cases of measles-induced immunosuppression lasting up to 6 months in the absence of virus replication, a more profound depletion of bone marrow progenitor cells during acute infection could account for a delay in the recovery of the immune system and slowed repopulation of the periphery.

It has been shown in rhesus macaque and cynologous monkey models of measles that the bone marrow is infected and contains high titers of virus [31, 32]. A recent report also showed productive in vitro infection of human bone marrow myeloid granulocyte-macrophage colony-forming cells (CFC-GM) [33]. The effect of measles on subtypes and/or maturation of bone marrow progenitors is unknown. An unexpected report of measles affecting bone marrow progenitor cells in vivo comes from analyses of patients suffering from Paget's disease, characterized by abnormal osteoclast resorption of bone followed by disordered bone formation. The presence of paramyxoviruses including measles has been demonstrated in bone marrow from pagetic patients [34]. Antibody screening has revealed expression of measles virus and respiratory syncytial virus nucleocapsid antigens in pagetic osteoclasts. Studies using reverse transcriptase polymerase chain reaction (RT-PCR) analyses have demonstrated either the presence of MV RNA in bone marrow osteoclast precursors (CFC-GM) or of canine distemper virus RNA in osteoclasts and osteoblasts [35, 36]. These observations clearly support the notion that measles can infect the bone marrow, and raise interesting questions about the possibilities of bone marrow persistence of measles in a small number of cases.

Since the rhesus macaque model suggests that a high number of infected cells are likely to be present in lymph nodes during acute measles, early events of immunosuppression may be due to mechanisms such as perturbation of function by direct infection [37, 38], cell cycle block of infected T lymphocytes, apoptosis of uninfected T lymphocytes by MV-infected DCs or inhibition of IL-12 and/or IFN-α/β synthesis. However, the long-term suppression that persists in the absence of detectable virus may be due to profound effects on bone marrow progenitor cell growth and differentiation.

HIV: the ultimate progressive suppression of the immune system

HIV, isolated only 2 decades ago, is responsible for severe immunosuppression which progresses slowly, providing an increasingly favorable terrain for opportunistic infections and reactivation of latent infections. It is the most dramatic of the immunosuppressive viruses, since in the absence of treatment, once a patient has progressed to acquired immune deficiency syndrome (AIDS), he or she will inevitably die from opportunistic infections. It is well documented that T lymphocytes expressing the CD4 molecule are the main targets of HIV infection, and their declining numbers in the peripheral blood reflect the progression of AIDS. Although CD4 T lymphocytes are important players in the immune response, their destruction is not thought to be the only cause of immunosuppression. HIV infection also results in APC defects that could explain the loss of CD4 responses early in HIV infection when T cell numbers are still within the normal range.

HIV, similarly to measles, can infect professional antigen-presenting DCs and impair their capacity to stimulate T cells with recall antigens or in a mixed lymphocyte reaction (MLR) in vitro. This effect de-

pends on the stage of differentiation of a DC, as DCs induced to mature and differentiate in vitro can be infected by HIV, but their antigen-presenting function is not impaired [39]. However, during HIV progression in humans, DC numbers are reduced in the peripheral blood of HIV patients [40]. A recent study reports that CD4 T lymphocytes require peripheral major histocompatibility complex (MHC) class II expression for survival. DCs, which express high levels of class II, may thus contribute to the maintenance of CD4 T lymphocytes. A decrease in functional DCs could lead to death of the CD4 T lymphocytes. Nevertheless, HIV-impaired APC function cannot solely account for the observed progressive immunosuppression, since bone marrow stem cells should continuously regenerate peripheral APCs. Bone marrow suppression, observed in HIV-infected individuals, may thus underlie HIV-induced immunosuppression. Over the course of disease, as is the case of RLV infection of mice, there is a progressive loss of the capacity to generate functional DCs from bone marrow progenitor cells, and the rate of hematopoietic regeneration is dramatically slowed [41–43].

There are conflicting reports about the capacity of HIV to directly infect CD34-expressing bone marrow progenitor cells [43, 44] (reviewed in [45]). Numerous studies have shown that the primitive CD34+ CD33− hematopoietic stem cells from HIV-1 patients are not infected with HIV, nor are they infectable in vitro. Thus, the HIV-induced suppression of hematopoiesis is unlikely to be a consequence of direct infection of stem cells. As the bone marrow stromal microenvironment contains numerous cell types which are essential to the growth of CD34+ progenitor cells, HIV infection of support cells has been suggested to explain the bone marrow suppression [45]. The stromal cells are a heterogeneous cell pool consisting of stromal epithelial cells, microvascular endothelial cells and macrophages, which all contribute to the regulation of cell growth and differentiation of CD34+ stem cells. Stromal epithelial cells appear resistant to HIV infection, whereas microvascular endothelial cells have consistently been shown to be infected by HIV in seropositive patients regardless of the stage of disease [46]. Bone marrow macrophages are also infected in vivo and in vitro by HIV. Many reports have suggested that the greatest impact of HIV on hematopoietic progenitor cell growth results from its capacity to infect these auxiliary bone marrow microvascular endothelial cells and/or macrophages. The mechanism may work via inhibition of growth factors and cytokines essential for hematopoiesis. This is illustrated by experiments showing that HIV-infected human stromal cell populations significantly decrease the ability of human as well as mouse hematopoietic precursor cells to form colonies in vitro [47]. The progressive worsening immunosuppression associated with AIDS may thus stem from the impairment of DC, macrophage and/or T cell regeneration due to the infection of bone marrow auxiliary cells supporting hematopoietic growth. Since later-stage lymphoid, myeloid and monocytic progenitor cells are infectable by HIV, their infection may compound the defect in regeneration of hematopoietic cell lineages.

In addition to the loss of CD4 T lymphocytes, APC dysfunction and/or lack of hematopoietic regeneration, other mechanisms have been put forth to explain HIV-induced immunosuppression. Apoptotic cell death has been suggested to generally weaken the immune response in HIV-infected patients. CD4 and CD8 T lymphocytes from HIV-infected patients are extremely sensitive to Fas-induced apoptosis. Furthermore, when quiescent nonactivated HIV-infected CD4 lymphocytes home to lymph nodes, it has been shown that signaling through the homing receptor induces apoptosis [48]. There are also reports that the envelope protein, gp120, and the tat protein of HIV can have immunosuppressive effects. Gp120 binds to uninfected CD4 cells and can induce a nonresponsive state by preventing CD4 interaction with the APCs [49]. Tat is a soluble virus protein that can induce apoptosis in uninfected cells [50, 51]. Increased secretion of certain cytokines such as IL-10 has also been suggested to suppress the immune response [52].

These peripheral events may all contribute to immunosuppression in the early stages when hematopoiesis is occurring properly and maintaining a relatively normal level of cellular regeneration. The collapse may arise when hematopoiesis falters and can no longer compensate for the other immunologic abnormalities. It is not yet clear what molecular event(s) lead to the final irreversible collapse.

Human cytomegalovirus: a persistent virus infection inducing a transient immunosuppression

Human cytomegalovirus, a member of the herpesvirus family, is another example of a human-immunodeficiency-inducing virus. CMV infects the majority of humans by adult age. Infection of individuals with normal immune responses causes an acute infection accompanied by transient immunosuppression. The immune dysfunctions improve to normal responsiveness over a period of weeks or months. The virus then establishes a latent infection with minor or no symptoms. In cases of acquired immunodeficiency such as HIV infection or transplantation, CMV can reactivate to cause severe disease. CMV is thus different from both MV and HIV in that CMV is a persistent infection which induces transient immunosuppression.

Several mechanisms have been put forward to explain CMV-induced immunosuppression. Early reports suggested that CMV could have a direct inhibitory effect on cytotoxic T lymphocytes [53, 54] or on monocyte function [55–57]. In vitro studies of monocyte antigen-presenting function have shown that monocytes from patients with CMV mononucleosis and normal monocytes infected in vitro are impaired in their ability to induce antigen-driven T-cell responses. Suppression of monocyte functions such as oxidative activity and phagocytosis has been observed both for infectious and ultraviolet (UV)-inactivated CMV [58]. Both infectious and UV-inactivated CMV are strong inducers of IFN-α/β in peripheral blood mononuclear cells (PBMC). Recent studies have shown that the in vitro CMV-triggered suppression of monocyte activation is due to the IFN-α/β produced by these cells [58]. Inactivation of IFN-α/β with neutralizing antibody greatly reverses the suppressive effect. The antibody treatment does not completely reverse the suppression, but because IFN type 1 encompasses over 20 isoforms of IFN-α and one of IFN-β, it is impossible to completely neutralize.

Another hallmark of CMV infection is the suppression of hematopoiesis in the bone marrow. The ability of bone marrow progenitor cells to differentiate and form colonies has been analyzed in vitro after infection with different isolates of CMV. It has been shown that whereas some wild-type field isolates could directly infect progenitor cells and impair their growth, others could only infect bone marrow stromal cells. This stromal cell tropism, reminiscent of HIV infection, profoundly inhibits in vitro progenitor cell colony growth by diminishing the production of certain growth factors [59]. In vitro supply of growth factors G-CSF, GM-CSF and IL-6 could overcome the stromal cell-induced suppression of progenitor cell growth [60]. The progenitor cells studied were cells expressing the CD34 and CD33 markers (fig. 2). Very recent studies seeking to identify the latent reservoir of CMV have shown that in vitro infection of a more primitive progenitor cell (CD34+ CD33−) gives rise to latent infection which can be detected by RT-PCR. Latent transcripts are not detected after infection of mature macrophages, DCs or lymphocytes. Latent infection of CD34+ CD33− progenitor cells has also been detected in bone marrow from naturally infected patients [61]. In light of these results, it would seem that the earlier work which detected CMV by immunofluorescence likely underestimated the infection capacity of the progenitor and/or stromal cells by CMV.

Therefore, CMV appears to be able to infect primitive progenitor cells as well as stromal support cells in contrast to HIV, which only infects auxiliary support cells. Viral infection of bone marrow may thus be the primary mechanism of CMV-induced immunosuppression.

Conclusions

MV, HIV and CMV provide three examples of virus infections which all induce generalized immunosuppression but have dramatically different outcomes. Table 1 summarizes the characteristics of the three infections. Theses viruses act by (i) dysregulating the early IL-12/IFN-α/β cytokine balance, (ii) disabling DC and/or macrophage function, (iii) producing immunosuppressive proteins and (iv) disrupting hematopoiesis. As discussed earlier, regulation of cytokines, which ensure a balanced immune response, must be finely tuned. It has been shown with both viral and parasitic infections that the presence of IL-12 and/or IFN-α/β is crucial for the proper development of a vigorous cellular immune response. Viruses which target hematopoiesis may completely devastate the immune system, as seen with HIV, or may establish benign latency, as with CMV. The reasons which determine these dramatically different outcomes are likely to be due to complex differences in the viral life cycle.

Table 1. Comparison of the nature of human immunosuppressive viruses.

Virus	Type of infection	Suppression	Suggested mechanisms	Data obtained
MV	acute phase/virus cleared	transient	1-Th1/Th2 imbalance 2-DC dysregulation 3-bone marrow-suppression 4-toxic protein: fusion	In vivo In vitro In vitro In vitro
HIV	persistent	progressive	1-CD4+ cell depletion 2-DC dysregulation 3-Th1/Th2 imbalance 4-bone marrow suppression 5-toxic protein: gp120/tat	In vivo/in vitro In vivo/in vitro In vivo In vivo/in vitro In vitro
CMV	persistent	transient	1-bone marrow suppression 2-macrophage dysfunction	In vivo/in vitro In vitro

Much but not all of the experimental data concerning virally induced immunosuppression has been obtained in vitro. However, the murine models of LCMV and RLV infections have confirmed that similar mechanisms are at work in vivo. Immunosuppression results not from a single mechanism of immune dysregulation but rather from an accumulation of immunological roadblocks that may begin minimally and undergo amplification as the immune response evolves.

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