Long-term non-progressive human immunodeficiency virus infection: new insights from the simian immunodeficiency virus model

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Introduction

Long-term non-progressors of human immunodeficiency virus (HIV) infection have recently become the subject of intensive research. This phenomenon probably reflects the multifactorial nature of the interaction between virus and the immune system. However, the early phase of infection, which seems to be critical for disease progression, can only be investigated properly in an animal model of HIV infection. In the simian immunodeficiency virus (SIV) model, the initial immunological and virological mechanisms which follow infection of macaques with defined SIV strains of different pathogenic potential can be studied. In macaques, an early virus-specific helper T cell response is associated with absence of disease progression. Furthermore, cytokine patterns and apoptosis of CD4 cells play an important role in early SIV pathogenesis.

General overview

Infection with HIV-1 in humans is normally characterized by severe immune dysfunction leading to the development of AIDS and death with a median time of 10 years. Disease progression is predominantly reflected by a decreased CD4 cell count. However, reports of healthy individuals, HIV-infected for more than a decade without any immune dysfunctions, are emerging (Levy, 1993). These long-term survivors of HIV infection have recently become the subject of intense research. From these people one might learn important lessons about the treatment of AIDS. Therefore, immunological (Greenough et al., 1994; Rinaldo et al., 1995) and virological (Greenough et al., 1994; Michael et al., 1995; Kirchhoff et al., 1995) mechanisms by which HIV infection is impeded in these individuals have been studied. However, the investigation of these parameters in long-term non-progressive humans is normally based on retrospective studies in selected patients. The early phase of infection can therefore only be analysed in HIV-infected infants. In these individuals, an early high virus load with sustained viraemia is usually accompanied by the inability to mount an effective immune response and rapid disease progression (D’Souza & Mathieson, 1996). Therefore, the balance between the immune system and virus replication in the early phase of infection may influence subsequent progression to AIDS or non-progression. To investigate this initial relationship in adult individuals with a fully developed immune system, animal models of HIV infection can be used. SIV infection of macaques is a practical and relevant animal model for HIV infection. The two viruses are genetically related and certain strains of SIV cause simian AIDS, which is very similar to the human disease (Kindt et al., 1992). In this model, early immunological events occurring after infection with defined immunodeficiency viruses can be studied. This will give new insights into mechanisms underlying individual resistance against development of AIDS in some HIV-infected humans.

Infection of macaques with immunodeficiency viruses

Since 1985 macaque monkeys have been used as animal models for AIDS research (Letvin et al., 1985). Most of the SIV isolates used for vaccine testing or pathogenicity studies induce an AIDS-like disease in macaques which leads to death within 2 years (Kindt et al., 1992; Letvin & King, 1990; Dittmer et al., 1994). During our on-going work on vaccine development we have infected over 50 naive rhesus macaques (Macaca mulatta) with different strains of pathogenic SIV with high replication capacity. Although some of these animals progress to disease more slowly than others, all macaques had to be killed because of AIDS developing within 3 years. Non-progression to AIDS seems to be a rare event in macaques infected with pathogenic SIV. However, several SIV isolates are pathogenic in some monkey species but apathogenic in others (Fultz et al., 1990; Cranage et al., 1992). Moreover, SIV can be experimentally attenuated to different extents. It has been shown that deletions in regulatory genes of SIV lead to reduced virus replication in vivo and subsequently to long-term non-progression of infected macaques (Kestler et al., 1991;
Hoch et al., 1995; Dittmer et al., 1995a). A similar mechanism has been suggested for HIV-infected non-progressing humans who harbour defective virus (Michael et al., 1995; Kichhoff et al., 1995). Moreover, HIV is infectious, but apathogenic, in some monkey species. Like HIV-1 in chimpanzees (Heeney, 1995), the slowly replicating HIV-2 leads to a persistent infection in cynomolgus macaques (Macaca fascicularis), but does not induce AIDS in these animals (Dittmer et al., 1994). In addition, the SIV model shows that low doses of pathogenic virus can lead to a latent infection in monkeys. In such animals, virus replication seems to be suppressed early after infection by a virus-specific cellular immune response (Dittmer et al., 1995b, c; Salvato et al., 1994). This observation is supported by reports on specific T cell responses in HIV-seronegative individuals exposed to HIV (Shearer & Clerici, 1996). To sum up, virological factors seem to play an important role in the establishment of non-progressive immunodeficiency virus infections. However, it has been reported that some SIV isolates replicate very efficiently, but do not cause disease, in defined monkey species, e.g. SIVsm in sooty mangabeys (Fultz et al., 1990) or SIVmac in baboons (Cranage et al., 1992). In these models, the mechanism of protection against disease remains obscure. In this context, host factors might play a critical role. Recently, Ashworth et al. (1995) found an association of major histocompatibility complex (MHC) class II expression with the course of disease in SIV-infected macaques. These results support the differences in the MHC class II-restricted CD4 cell response in animals progressing or non-progressing to disease. In addition, Bontrop et al. (1996) reported that polymorphism of the MHC class I gene influenced the course of disease in SIV-infected animals. These findings point to a key role of cytotoxic T cells in controlling virus replication. However, until now intrinsic host factors that influence progression to simian AIDS have been poorly understood. On the other hand, the initial balance between SIV replication and the induced immune response might be a critical step in the development of AIDS in macaques. Therefore, early immunological responses of macaques infected with immunodeficiency viruses of different pathogenic potential have to be compared carefully.

**Similar CTL and antibody responses in non-progressors and progressors during acute SIV infection**

Virus-specific cytotoxic T cells (CTL) and neutralizing antibodies are the major immune mechanisms that can control virus replication in the host. It has been suggested that HIV-specific CTL might play an important role in controlling virus replication, therefore preventing disease in long-term non-progressors (Greenough et al., 1994; Rinaldo et al., 1995). However, in many HIV-infected individuals, an initial decrease in the virus load has been seen before CTL were detectable (D’Souza & Mathieson, 1996). In the SIV model, virus-specific CTL directed against several polypeptides of SIV have been described (Miller et al., 1990; Voss et al., 1992b). These CD8-positive and MHC class I-restricted cells that could be detected after specific or non-specific in vitro stimulation appeared very early after infection (within weeks). In addition, SIV-specific CTL seem to be associated with clearance of viraemia from the peripheral blood and lymph nodes of infected animals (Reimann et al., 1994). However, so far no clear correlation has been found between the initial induction of CTL and progression to disease in SIV-infected macaques (Voss et al., 1992b). Furthermore, macaques infected with apathogenic HIV-2 (Voss et al., 1992a) or attenuated SIV (Dittmer et al., 1995a) develop early virus-specific CTL responses comparable to those of macaques infected with pathogenic SIV.

With regard to the humoral immune response, a relationship between HIV-1-specific antibody reactivity and disease progression in HIV-1-infected humans has not been established (D’Souza & Mathieson, 1996). Controversial findings were also made by comparing early SIV-specific antibody responses from animals infected with pathogenic or apathogenic SIV. In some of these studies the titres of binding antibodies were higher in the animals harbouring more virus

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* Unspecific marker for an activated immune system (Fuchs et al., 1988).
† Antigen-specific Th proliferation.

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**Table 1. Early immunological findings in immunodeficiency virus-infected macaques progressing to AIDS or non-progressing**

Key: +, increased; −, decreased; =, unchanged; Ab, antibodies; CTL, cytotoxic T cells; Th, helper T cells; IL, interleukin; IFN, interferon.
and subsequently progressing to AIDS (Marthas et al., 1993). In contrast, it has also been reported that long-term non-progressors of SIV infection developed a pronounced antibody response (Hoch et al., 1995; Stahl-Hennig et al., 1996). Moreover, similar titres of binding (Benveniste et al., 1996a) and neutralizing (Norley et al., 1996) antibodies against SIV were observed in monkeys infected with pathogenic or apathogenic SIV isolates.

Therefore, in the SIV model the virus-specific CTL activity and antibody response in the early phase of infection could not clearly distinguish between animals progressing to AIDS or those staying healthy (Table 1).

**Early virus-specific Th response is associated with long-term non-progression**

In contrast to their CTL and antibody reactivity, progressors and non-progressors show striking differences in the proliferative response of T cells early after infection. The proliferating cells were CD4-positive and their antigen recognition was MHC class II-DR restricted (Dittmer et al., 1994; Voss et al., 1992b). These helper T cells (Th) are known to be the predominant host cells for HIV and SIV infection and replication. Although HIV infection is usually associated with a severe Th loss, virus-specific Th have been described in the asymptomatic phase of HIV-infected humans (Schrier et al., 1989). However, progression to AIDS leads to a progressive Th defect in infected individuals (Clerici & Shearer, 1993). A similar Th dysfunction in response to recall antigens and mitogens could be observed after infection of macaques with pathogenic SIV (Mills et al., 1993; Dittmer et al., 1994, 1995a).

In this model, Th dysfunction was correlated with the pathogenic potential of the virus used for infection (Fig. 1). Animals infected with pathogenic SIV did not develop a virus-specific Th response (Dittmer et al., 1994). Furthermore, a vaccine-induced Th reactivity was abrogated after SIV infection in vaccine failures (Dittmer et al., 1994; Voss et al., 1993). This Th dysfunction might be due to an SIV-induced destruction of antigen-presenting cells, e.g. follicular dendritic cells (Joling et al., 1992; Rosenberg et al., 1994; Persidsky et al., 1995). In contrast, all animals infected with attenuated SIV mutants developed a strong or intermittent virus-specific Th response in the early phase of infection (Hoch et al., 1995; Dittmer et al., 1995a). Some of these animals developed AIDS-like symptoms after a very long asymptomatic period, whereas some stayed persistently healthy. In addition, macaques infected with the apathogenic HIV-2 developed an early virus-specific Th response which was associated with a subsequent decrease in virus load (Dittmer et al., 1994). Recently, we were able to investigate a few animals that were infected with pathogenic SIV, but suppressed virus replication and did not show any sign of immunodeficiency. Similar to macaques infected with apathogenic immunodeficiency viruses, these animals developed an early virus-specific Th response, whereas several other monkeys infected with the same virus did not, and progressed to AIDS.

It has been suggested that high numbers of lymphocytes undergoing programmed cell death (apoptosis) might contribute to the dysfunction and loss of CD4 cells seen in HIV-infected humans (Ameisen, 1994). However, in the SIV model for HIV infection, a large number of apoptotic lymphocytes can be found in both progressors and non-progressors. Macaques infected with pathogenic SIV, attenuated SIV (deleted in nef) (Estaquier et al., 1994) or apathogenic HIV-2 (Dittmer et al., 1996) have been investigated during acute infection. Animals infected with pathogenic SIV show an increased number of apoptotic CD8 and CD4 cells. In contrast, animals infected with apathogenic immunodeficiency viruses had elevated levels of apoptosis in the CD8 cell fraction only (Estaquier et al., 1994; Dittmer et al., 1996). Therefore, the

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**Fig. 1. Schematic diagram of virus-specific T cell responses in macaques infected with different immunodeficiency viruses.** The Th response early after infection in animals progressing to AIDS or non-progressing is shown as the mean of stimulation indices (Dittmer et al., 1994) from macaques of each group (n ≥ 6). (a) Naive macaques or SIV vaccine failures develop an unresponsiveness of their Th after infection with SIV wild-type. These animals subsequently progress to AIDS. (b) In contrast, macaques infected with attenuated SIV or those exposed to low doses of SIV mount an early virus-specific Th response and become long-term non-progressors. In addition, naive macaques and vaccine failures infected with the low replicating HIV-2 initially developed a specific Th activity and did not progress to AIDS.
persistent Th response of non-progressors seems to be associated with the lack of apoptosis in CD4 cells. On the other hand, the apoptotic cell death of activated CD4 cells in progressors appears to play a critical role in AIDS pathogenesis. This is supported by Clerici et al. (1996), who reported that antigenic stimulation induces cell death in lymphocytes of HIV-positive donors. The apoptosis of CD8 cells in immunodeficiency virus-infected monkeys might be compensated for by an efficient CD8 cell renewal (Heeney, 1995). It has been suggested that HIV-associated apoptosis might be induced by disruption of the cytokine network. The SIV model revealed an altered cytokine production of macaque lymphocytes during the acute phase of infection. In lymphocytes from animals progressing to AIDS, the Th1-like IFN-γ was down-regulated early after infection, whereas the Th2-like IL-10 and IL-6 were up-regulated (Benveniste et al., 1996a, b). In contrast, during acute infection INF-γ was up- and IL-10 was down-regulated in non-progressors. This has been shown for animals infected with attenuated SIV (Benveniste et al., 1996a) and for animals that were able to suppress replication of pathogenic SIV (M. Spring & U. Dittmer, unpublished results). The predominant loss of Th1-like cytokine expression in animals infected with pathogenic SIV might contribute to the increased number of apoptotic CD4 cells and the subsequent Th dysfunction. The role of chemokines and their receptors, which are highly important in HIV infection and pathogenesis (Bates, 1996), have not been evaluated in SIV-infected monkeys so far.

The SIV model for HIV infection reveals that the early Th response against immunodeficiency virus infections is critical for the pathogenic consequences in monkeys (Table 1). The Th dysfunction, probably associated with modified cytokine expression and CD4 cell apoptosis, is the first immunological alteration pointing to disease development. In contrast, an early virus-specific Th response was associated with a delayed disease progression. The relationship between immune response and virus replication seems to be predominantly determined by the phenotype or virulence of the infecting virus.

Conclusions

Implications for vaccination and therapy against AIDS

It has been reported by Putkonen et al. (1990) that infection of macaques with apathogenic HIV-2 protected these animals against the pathogenic consequences of an SIV superinfection challenge. In other vaccine experiments, macaques infected with attenuated immunodeficiency viruses developed a rapid secondary Th response after superinfection with pathogenic SIV. Although only some of these animals were protected against the SIV infection, all of them became long-term non-progressors (Petry et al., 1995; Stahl-Hennig et al., 1996). Despite a high virus burden in macaques directly after infection with apathogenic immunodeficiency viruses, the subsequent drop of virus load enabled the immune system to establish an efficient antiviral Th response. Although the effector mechanism remains speculative in this model, the early antigen-specific Th response was associated with low replication of pathogenic SIV after superinfection and delayed disease progression. In contrast to these findings, it has been reported that attenuated SIV can revert to virulent phenotype in macaques after repair of the attenuated lesion (Whatmore et al., 1995; Dittmer et al., 1995a). These animals had normally developed virus-specific Th in the early phase after infection. Paradoxically, after reversion the SIV-specific immune response was inefficient at preventing the onset of immunodeficiency in the animals. Furthermore, the Th response of these animals was abrogated after reversion (Dittmer et al., 1995a).

It has been reported that SIV-specific Th induced by low doses of infectious SIV might confer protection against a high-dose challenge (Salvato et al., 1994; Clerici et al., 1994). This is in line with the hypothesis that humans exposed to low doses or defective strains of HIV develop virus-specific Th and are subsequently resistant to the consequences of HIV superinfection (Clerici & Shearer, 1993). In addition, it has been reported for human cytomegalovirus that cytokines released by Th clones play an important role in antiviral activity (Davignon et al., 1996). This could also be the case in the early phase of SIV and HIV infection.

Recent studies using the SIV model have shown that an early reduction of virus burden due to immune globulin or drug therapy can prolong the asymptomatic phase in SIV infection (Haigwood et al., 1996; Tsai et al., 1995). Passive antibody therapy has also been studied in other retroviral infections. In Friend murine leukemia virus-infected mice the recovery from virus infection, after administration of virus-specific antibodies (Hunsmann et al., 1975), depends on T cell activity (Hasenkrug et al., 1995). In this model, specific Th seem to play the critical role for retroviral immunity (Hasenkrug et al., 1996). The Th response of immunodeficiency virus-infected monkeys not progressing to AIDS underlines the importance of an early T cell response in retrovirus infections. The reduction of virus burden during acute infection seems to enable the host immune system to mount a virus-specific Th response, which could lead to recovery from virus infection or disease development. Therefore, a modulation of the immune system during the early phase of HIV infection might at least delay disease onset. Thus, as suggested by Ho (1995), asymptomatic HIV-1 infection has to be treated ‘early and hard’. In this context, the Th response is a potent parameter to determine the outcome of therapeutic studies in immunodeficiency virus infection (Clerici et al., 1992). Moreover, understanding immunological mechanisms responsible for progression to AIDS or non-progression will also provide clues for AIDS vaccine development. Studying the as yet unanswered questions in the SIV model will most likely substantiate progress in HIV research in the near future.
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References


