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Immune correlates of protection from HIV infection and AIDS

Jonathon L. Heeney, Claudine Bruck, Jaap Goudsmit, Luc Montagnier, Alan Schultz, David Tyrrell and Susan Zolla-Pazner

Protective immunity to AIDS may be considered as a spectrum of immune responses that elicit protection from infection and protection from disease progression. These responses can be further considered as either naturally acquired or vaccine-induced (Box 1).

Examples of individuals with naturally acquired immunity to human immunodeficiency virus (HIV) infection are now evident. These include certain cases of partners of seropositive individuals and prostitutes, who are repeatedly exposed but protected from infection, as well as some cases of babies born to infected mothers. There are few examples of humans who have acquired natural resistance to the development of AIDS following infection with virulent inocula of HIV-1, in contrast to the vast majority of natural-lentivirus-infected African nonhuman primates (NHPs). The immune mechanisms used by these particular humans and NHPs to prevent disease progression in the face of chronic infection are of particular interest.

Vaccine- or immunotherapeutic-induced immunity sufficient to protect from infection and/or disease has been observed in NHP model studies. Such preclinical efficacy studies are helping to define important immunological milestones for the measurement and evaluation of vaccine candidates in clinical trials. The number of preclinical examples of protection from infection and disease is accumulating. In these cases, there has been considerable debate concerning which arm of the immune system appears to be more important in eliciting the type of protection observed. The following summary highlights the discussions that arose at the workshop during the intercomparison of studies of natural and acquired immunity and portrays the emerging trends, while emphasizing current questions that remain to be addressed in future studies (Box 2).

At an international workshop, the immune responses observed in cases of protection from HIV infection or disease progression were discussed. An understanding of the immunological mechanisms associated with protection from lentivirus infection and disease is likely to have an important impact on vaccine design and new therapeutic strategies.*

Host-virus interactions

It is clear that the outcome of exposure to HIV and the subsequent development of AIDS or survival in both human and NHP hosts is dependent on a complex interaction between virus and host (the latter being significantly influenced by environmental factors such as concurrent infections and/or stress). A plenary debate at the XIth International Conference on AIDS confirmed an important interplay of both viral (D. Ho, New York, NY) and host (C. Pantaleo, Bethesda, MD) factors.

With regard to host factors, several different clinical settings have been examined. A number of studies made the point that the tremendous heterogeneity of the human population in terms of disease progression was a reflection of the genetically diverse outbred human population; the survival time of individuals of an infected population is reminiscent of a bell-shaped curve with each extreme representing a small number of individuals that are either rapid progressors (RPs) or long-term non-progressors (LTNPs).

In addition, virus variables play a significant role in determining disease progression. Infection by attenuated viruses may occur¹ and a unique case with a predominance of defective proviral sequences (D. Schwartz, Baltimore, MD) portrayed the rare circumstances in which infected individuals remain

healthy with normal or stable CD4⁺ T-cell counts. Furthermore, the initial virus strain that an individual becomes infected with may therefore greatly influence the nature of the disease course, even in the case of subsequent exposure to more virulent isolates². The significance of 'peak' versus 'steady-state' levels of virus load was debated (J. Goudsmit, Amsterdam), and recent data have confirmed that steady-state measurements are important predictors of survival³. The biological properties of the virus strain (e.g. replication potential, syncytia induction and tropism of virus for macrophages or dendritic cells) might influence both infection and disease course. With regard to biological variants of HIV-1, the recent finding that certain chemokine receptors act as specific co-receptors for syncytium-inducing (SI) (fusin)⁴ and non-syncytium-inducing (NSI) (CC-CKR-5)^{5,6} variants has brought together different observations from several areas of research and opened a very active new direction in AIDS research. The β -chemokines RANTES, macrophage inflammatory protein 1 α (MIP-1 α) and MIP-1 β (which bind CC-CKR-5) inhibit HIV-1 (Ref. 7) in a similar manner to the natural suppression achieved by soluble factors from CD8⁺ lymphocytes (CD8-SF). These factors were first shown to inhibit infection in infected humans⁸, especially LTNPs, and infected AIDS-resistant NHPs (Ref. 9). These findings emphasize the intricate host-virus relationship of this disease and suggest immune mechanisms for observations such as repeated sexual exposure, concurrent sexually transmitted diseases and relative resistance to infection.

It is becoming more apparent that there is an important interaction between the route of exposure, certain viral-virulence factors and the cell-free or cell-associated nature of the viral inoculum¹⁰. At the time of exposure, infection is influenced by dose, concurrent

genital infections, as well as host factors such as genetic background (F. Plummer, Nairobi; D. Mann, Frederick, WA). Immunological status (i.e. naive, quiescent or activated) or possible pre-existing immunity of the host resulting from previous exposure¹¹ are important host factors that may not only influence infection but may also influence virus-load peaks before seroconversion and virus-load levels thereafter.

Naturally acquired immunity

Protection from infection

A number of clinical study groups were examined and compared. They included various cohorts of seronegative high-risk individuals, and various factors that could afford protection from infection were investigated.

A specific group of prostitutes in Kenya was demonstrated to remain HIV-1⁻ despite repeated exposure and high-risk activity (Plummer). Members of this group were found to have cellular immune responses to several regions of the virus and to have an interesting familial association. The presence of HIV-specific cytotoxic T lymphocytes (CTLs) in exposed seronegative prostitutes has been demonstrated¹².

Uninfected partners of seropositive individuals have also been studied. In addition to having cellular immune responses indicative of primed T helper 1 (Th1)-type immune responses¹¹ (M. Clerici, Milan) and/or CTL responses¹², proliferative immune responses to the C5 region of gp120 were found in some patients (A. Beretta, Milan). Such individuals are reported to have anti-CD4 antibodies and antibodies that cross-react with human major histocompatibility complex (MHC) HLA. Other factors such as the virological and immunological status of the donor may also reduce the risk of virus transmission.

In one particular study, two potential donor groups were studied: LTNP's and non-transmitting mothers. The presence of autologous neutralizing antibodies, slow/low NSI virus, and a polymorphic site at the tip of the V3 loop correlated with a lower risk of transmission as well as disease progression (G. Scarlatti, Milan).

Since then it has been reported that switching the amino acid sequences of the

Box 1. Examples of protective immunity

(1) Naturally acquired:

(a) Protection from infection (HIV)

- Natural resistance
- Acquired resistance
 - Prostitutes who practise unprotected sex
 - Intravenous-drug users
 - High-risk partners of seropositives
 - Seroreversion of infected infants

(b) Protection from development of disease (AIDS)

- Long-term non-progressors
- HIV-1-infected chimpanzees
- SIVsm-infected sooty mangabeys
- SIVagm-infected African green monkeys

(2) Vaccine-induced:

(a) Examples of vaccine protection from infection

- HIV-1-vaccinated chimpanzees protected from HIV-1 challenge
- HIV-1-vaccinated macaques protected from SHIV challenge
- SIV-vaccinated macaques protected from SIV challenge

(b) Examples of vaccine protection from disease

- Live-attenuated-vaccine studies
- SIV-Ig immunotherapy

Abbreviations: HIV, human immunodeficiency virus; Ig, immunoglobulin; SHIV, simian-human immunodeficiency virus; SIV, simian immunodeficiency virus.

Box 2. Questions to be addressed in future studies

- (1) Can a host clear an established HIV-1 infection? Are CMI-positive seronegative partners of infected persons persistently infected in some cryptic way?
- (2) Are immune responses in seronegative high-risk individuals responsible for protection or an indication of previous limited or abortive infection?
- (3) What are the roles of chemokines and CD8-suppressor factors *in vivo* in infection, virus-specific immune regulation and disease progression?
- (4) Is the controversial shift from a Th1- to a Th2-type response a cause or effect of disease progression?
- (5) What is the nature of protective antibodies versus enhancing antibodies?
- (6) Are levels of CTL responses correlated with control of virus replication? Under which circumstances do CTLs contribute to AIDS pathogenesis?
- (7) Are low primary CTL responses seen in patients with low CD4⁺ counts a result of deficient Th responses?
- (8) Are immune responses seen in LTNPs a cause or consequence of low virus load?
- (9) Can clinical outcome be modified by immunotherapeutic intervention?
- (10) Does sterilizing immunity actually occur in preclinical vaccine-efficacy studies or are there transient infections?
- (11) Can vaccines that do not protect from infection protect from disease progression? What type and to which viral antigens are immune responses required to slow or halt disease progression?
- (12) Will approaches to reduce virus load allow full and normal reconstitution of the immune response?

Abbreviations: CMI, cell-mediated immunity; CTL, cytotoxic T lymphocyte; HIV, human immunodeficiency virus; LTNPs, long-term non-progressors; Th¹, T helper 1.

V3 region of SI and NSI viruses changes their co-receptor specificity for fusin or CC-CCR-5 (Ref. 13). The earlier report that the CC chemokines RANTES, MIP-1 α and MIP-1 β block infection of certain primary HIV-1 isolates⁷ led to the identification of the CC-CCR-5 receptor as an important co-receptor for NSI HIV-1 isolates^{5,6,12-15}. Interestingly, it has also been demonstrated that some high-risk sexually exposed individuals may have CD4⁺ lymphocytes that are relatively resistant to HIV-1 infection¹⁶, and this resistance correlated with the activity of β -chemokines⁷. It would be useful to determine the type of virus that these individuals were exposed to, and if the molecules that bind to fusin can block SI virus entry.

Finally, cases of transient infection (infection with subsequent clearance) were considered. Three types of immune reactivities were observed in high seronegative, transiently expressed, virus-isolation-positive patients: anti-CD4 antibodies, anti-HLA antibodies and Th-type responses to envelope peptides. Furthermore, higher prevalences of specific MHC transporter associated with antigen processing (*Tap*) variants, and CD8⁺ cells that expressed CD25⁺ antigen were apparent in these individuals (Mann).

Recent findings report that some uninfected individuals with a high risk of HIV-1 infection are homozygous for a 32-base-pair deletion of their CC-CCR-5 genes (CC-CCR-5 Δ 32)^{17,18}. This results in a loss of extracellular expression of this receptor.

Protection from disease

In HIV-1-seropositive cohorts, approximately 5% of infected individuals remain healthy without evidence of disease progression. Infection with attenuated virus isolates is documented in very rare cases, but for the majority of long-term survivors (LTSs) or LTNP, this appears not to be the case. Some infected individuals with slow disease progression are heterozygous for CC-CCR-5 Δ 32 (Ref. 19). In studies of resistance to disease, seropositive rapid progressors (RPs) are often compared with LTNPs. Central to the discussion of the host's susceptibility or resistance to disease is the immunoregulatory function of the MHC. In humans, certain MHC class I alleles when associated

with *Tap2.3* genes were reported to correlate with increased disease-free interval, whereas *Tap* associations with other class I or II markers were correlated with rapid progression of disease (Mann)²⁰. In strictly controlled studies in rhesus monkeys infected with a particular strain of simian immunodeficiency virus (SIV), the presence of a certain MHC Mamu-A26 was associated with slower progression to AIDS (R. Bontrop, Rijswijk).

In LTNPs, MHC class I-restricted CD8⁺ CTLs have been shown to be generated against various viral targets. A correlation of CTLs with low virus load was implied, but it was an inconsistent direct or inverse relationship when considered longitudinally and depended on the CTL targets of the virus studied. A greater number of CTL precursors were observed in LTNPs (Ref. 21) than in RPs (J. Safrit, New York, NY). By contrast, an absence of primary CTL Gag responses was correlated with an increased relative risk of progression to AIDS (Y. Rivière, Paris)²². In addition to CD8⁺ CTLs, CD8⁺ cells that release HIV-suppressing factors similar to CD8⁺ T-cell antiviral factor (CAF)²³ were shown to be present in several examples of protective immunity, as illustrated by several groups in different systems. At the International Conference on AIDS, J. Levy (San Francisco, CA) stressed that CAF (Ref. 8) was CD8⁺-cell specific and its activity was greater in LTNPs than in progressors; this is in contrast to the β -chemokines⁷ (for review, see Ref. 24). Furthermore, important questions arose concerning the potential pathogenic effect of CD8⁺ CTLs in the destruction of lymphoid architecture⁹ in chronic HIV infection, and the possible interplay of CD8-SF in downregulating deleterious CTL responses.

With respect to MHC class II-related events, studies of the effects on Th-cell activation, apoptosis and anergy as well as production of Th1- and Th2-type cytokines and their relationship with disease progression were presented. Evidence supported a shift from a Th1- to a Th2-type response (Clerici)¹¹, but *in vivo* experimental proof is still required. Interestingly, HIV-1 was shown to replicate preferentially in Th2 cells²⁵, and crosslinking of upregulated CD30 on these cells potentiated virus replication (S.

Romagnani, Florence). An increase in generalized immune activation occurs in HIV infection as determined by increased MHC class II, CD45RO⁺, and CD38⁺, Th2-type-cytokine production, anergy and apoptosis. As with immune activation, apoptosis is found to be generalized and not restricted to CD4⁺ cells (M.-L. Gougeon, Paris). In general, these changes are not observed in natural-lentivirus-infected species, which are relatively resistant to AIDS.

Finally, there was considerable debate about possible natural-resistance mechanisms in African NHPs. In particular, it was noted that in cases of asymptomatic lentivirus infections with no evidence of disease progression, there was preservation of lymph-node architecture with an intact environment of MHC class II antigen-presenting cells and Th cells⁹. Although there was a consensus about the presence of virus-inhibiting soluble factor(s) in lentivirus-infected human LTNPs, chimpanzees (J. Heeney, Rijswijk), sooty mangabeys (A. Ansari, Atlanta, GA), these factors had only been characterized to any degree in humans (β -chemokines)⁷ and African green monkeys (interleukin 16)²⁶.

Vaccine-induced immunity Protection from infection

The role of neutralizing antibodies in protection of chimpanzees from cell-free laboratory strains of HIV-1 administered i.v. have been clearly demonstrated²⁷ (K. Murthy, San Antonio). There was considerable debate about whether effective, broad neutralizing antibody responses to field isolates may be obtained, and to which regions of the HIV-1 envelope these should be directed. Vaccination with envelope-based vaccines induces neutralizing antibodies to both linear and discontinuous epitopes primarily within the V2 and V3 regions. The use of truncated forms may broaden immunity to include V1/V2 regions, responses that correlate with neutralizing titre and crossreactive neutralizing responses in rodents (J. McKeating, Reading). Furthermore the state of activation of the target cell appears to have a significant effect on the efficacy of neutralizing antibodies²⁸ (S. Zolla-Pazner, New York, NY).

S-L. Hu (Seattle, WA) discussed current vaccine strategies: 'priming' with recombinant viruses that express HIV-1 (or SIV) *env* followed by subunit boosting appears to be one of the most effective ways of achieving protection from cell-free i.v. challenge. In the SIVmne model, vaccination with *gag-pol* alone showed that *env* was a necessary component for vaccine protection from infection; however, subunit *env* alone was not sufficient for protection despite similar levels of neutralizing antibodies being achieved. There remains considerable debate concerning whether true sterilizing immunity was achieved, or whether limited virus replication occurred before infected cells and virions were cleared.

No immunological correlate of protection was found in vaccinated chimpanzees challenged i.v. with infected blood mononuclear cells from another HIV-1-infected chimpanzee. In a similar study, vaccinated rhesus monkeys were found to be protected from infected cells when an MHC class I allele was shared between the donor and recipient¹⁰. Furthermore, CTLs were found in three out of four of the protected animals, which strongly implicated an involvement of CD8⁺ CTLs in protection from infected cells. Interestingly, CTLs to *gag* were detected only after challenge in vaccinated animals, supporting the idea of limited virus replication before immunological clearance was achieved (Heeney). Important advances in elucidating protective mucosal immunity have also been made. Protective mucosal immunity was shown to be elicited by targeted immunization of iliac lymph nodes in rhesus macaques. Protection from SIV infection was found to correlate with an increase of IgA-secreting cells, CD8-suppressor factor, RANTES and MIP-1 α in the iliac lymph nodes²⁹.

Protection from disease

Several studies pointed to the possible benefit of vaccination or immunotherapy to reduce virus load and possibly to slow or halt progression of disease. Studies in HIV-1-*env*-vaccinated chimpanzees have shown that in the case of infection, virus load can be significantly reduced²⁷. In addition, in the SIVmne model, although *gag* and *pol* alone

are insufficient for inducing sterilizing immunity, they were shown to be effective in reducing virus load (Hu). Furthermore, vaccination of rhesus monkeys with vaccinia recombinants containing only SIVmac *nef* resulted in a beneficial effect in reducing virus load that inversely correlated with CTL-precursor frequency (F. Gotch, London)³⁰. Another approach using a *nef*-defective SIVmac strain of live attenuated vaccine in rhesus monkeys, revealed that recipients challenged with wild-type SIVmac were resistant to infection with the challenge strain. By contrast to non-vaccinated SIVmac-infected controls, vaccinees maintained Th-cell responses (G. Hunsmann, Göttingen). Although none of these studies reached a clinical endpoint, these data suggest that a beneficial effect in humans may be achieved since virus load is an important marker of disease progression.

The role of antibodies was also examined. Broad cross-neutralizing antibody titres were shown to be associated with slow disease progression and low risk of transmission in HIV-2-infected macaques (E-M. Fenyo, Stockholm). The role of antibodies in slowing disease progression was elegantly demonstrated in an SIV model: in cases where SIV-immunoglobulin was administered shortly after experimental SIV infection i.v., recipients maintained lower virus loads and survived longer than untreated controls (N. Haigwood, Seattle, WA).

Emerging trends

Accumulating numbers of reports suggest that repeated sub-infectious low-dose exposure to HIV may elicit protective immunity. However, this observation needs rigorous evaluation to differentiate between: (1) individuals that have an existing natural resistance to infection and those that have acquired immunity by exposure; and (2) individuals that have acquired immunity and are truly uninfected and those that have a cryptic low-level or local infection. Cases of reported clearance of viral infection are of considerable importance; these cases need to be well documented and the immune responses as well as the virology require careful long-term follow-up.

It is apparent that the disease course may be established or greatly influenced by events immediately post-infection, which establish virus-load levels either before or after seroconversion. Current data suggest that in order to prolong survival, effective pre-existing or acquired immunity in this early period is very important. Passive immunity may be effective in this context, but must be established in a manner that will protect the immunological infrastructure from immunosuppressive effects of the virus and that allows effective *de novo* host-immune responses. Effective CTL responses to multiple epitopes may be important for reducing cell-associated virus load early after infection. If infection is not resolved to a low level, CTLs may possibly contribute to the immunopathogenesis of the disease. The roles of CD8-suppressor factors and HIV-inhibitory chemokines in protective immunity and the pathogenic process *in vivo* are now in need of elucidation. Protective immunity in the presence of HIV-1 infection appears to depend on intact Th responses that are responsible for primary cellular as well as humoral responses. Current trends suggest that vaccines intended for protection from HIV infection must be able to induce host responses that effectively limit extracellular viremia and effect clearance of virus-infected cells, while promoting primary host responses to new viral epitopes.

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MHC and behavior

Nicholaus Zavazava and Frank Eggert

The major histocompatibility complex (MHC) has been the subject of study for several decades. Much interest has focused on its regulation of the immune response, and most immunologists and biologists consider the function of the MHC to lie in immune defense. MHC polymorphism appears clearly to favor this simplistic view but, from an evolutionary point of view, the MHC has a much broader and universal function. The use of molecular genetic techniques has recently led to the discovery of even more new genes within the MHC. In mice, 58 nonclassical MHC class I genes, pseudogenes and gene fragments have been identified. Their role is not yet understood, but their lack of polymorphism suggests that they possess more-generalized functions, if any. In addition, olfactory-receptor-like genes have been recently described in the human and mouse class I regions.

Most work on the major histocompatibility complex (MHC) has concentrated on its role in immunological defense. At a recent meeting, the focus was on behavior. Psychologists, geneticists and immunologists discussed data that show that behavior is, in part, MHC determined.*

The major feature of the MHC is its extraordinary genetic diversity, which seems to be selectively maintained in contemporary natural populations, although the strength and nature of this selection are currently unclear¹. Because of the critical role played by proteins encoded by the MHC in immune recognition, it is generally assumed that some form of parasite-driven selection takes place². However, the high degree of hetero-

zygosity found in natural populations of most species seems to be promoted by non-disease-based selection, such as mating preferences and selective block of pregnancy.

Lewis Thomas was the first to speculate that the MHC might play a role in social behavior as an expression of genetic individuality, but he failed to explain how and why it may be involved.

Olfaction, kin recognition, behavior and the MHC

Early studies into the external expression of the MHC demonstrated disassortative mating according to MHC type in some congenic strains of mice³. A number of studies from different laboratories have subsequently revealed that the MHC is associated with the expression of olfactory cues in mice, rats and humans⁴. In mice, these signals contribute to the phenomenon of imprinted