What’s New in HIV/AIDS

Protective Immunity in HIV Infection: Where Do We Stand?

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In the face of a global epidemic of HIV/AIDS with the majority of individuals living in developing countries, a protective vaccine seems the foremost goal. As this is not within imminent reach, the other option would be an immunotherapy that prolongs the asymptomatic phase of infection. The basis for such a therapy is to understand the correlates of protective immunity against HIV. Here we present the most recent advances regarding selected parts of the immune response towards HIV.

HIV-1 Superinfection

During the past years, a number of reports have described HIV-1 superinfection in human subjects, defined as the reinfection of an individual with a second heterologous strain of HIV-1. The first published report described intersubtype superinfection in two injection-drug users from a prospective cohort of seronegative drug users in Bangkok, Thailand [1]. Subtype-specific immune responses were initially directed only against the primary virus and cross-subtype immune responses were limited or absent in both cases studied. An additional report about intersubtype superinfection demonstrated that superinfection led to rapid disease progression [2]. The most dramatic example though is the case of intrasubtype superinfection – clade B in both cases – with a clinical disease course that showed control of viremia before superinfection and disease progression after superinfection [3]. As reason for the disease progression, it could be shown that the second virus differed by only 12% at the amino acid level from the first virus. But this difference led to a loss of about 50% of the targeted T-cell epitopes. These reports have challenged the assumption that HIV-1-specific immune responses generated during primary infection are protective against subsequent infection and have raised concern, not only with respect to HIV-1-positive individuals engaging in unsafe sex but also from the standpoint of developing effective vaccines.

Cytotoxic T-Lymphocytes (CTL) Escape Mutation and Reversion after Transmission

As the understanding of escape mutations as a mechanism of viral immune evasion advances, the question becomes increasingly important as to what happens to these mutations once they are transmitted to a genetically different environment. A few years ago, Goulder et al. [4] showed that an escape mutation within an HLA-B27 restricted epitope in the mother can be transmitted to the B27+ child who then cannot make an immune response towards this epitope. Just recently several papers have been published regarding this question. In three cases, the mutated epitope reverted back to the wild-type sequence after transmission into a different genetic background [5, 6] (Allen TM et al.: Selection, Transmission and Reversion of an Antigen Processing Cytotoxic T-Lymphocyte Escape Mutant in Human Immunodeficiency Virus Type 1 Infection. J Virol in press). This shows that escape mutations can render HIV less fit and prone to mutate back when the immune pressure no longer exists.

CTL Escape Leading to Altered Antigen Processing

So far, viral escape mutations in response to immune pressure by CD8 T cells have been de-
scribed as mutations within the epitope interfering either with binding to the major histocompatibility complex (MHC) class I molecule on the antigen-presenting cell or the T-cell receptor on the T cells. Mutations in the flanking regions of epitopes leading to an inability of the cells to process peptides correctly have been postulated for a long time. In HLA-B57+ HIV-infected persons, immune selection pressure leads to a mutation from alanine to proline at Gag residue 146 immediately preceding the NH(2) terminus of a dominant HLA-B57-restricted epitope, IS-PRRTNAW. Although N-extended wild-type or mutant peptides remained well recognized, mutant virus-infected CD4 T cells failed to be recognized by the same CTL clones. The A146P mutation prevented NH(2)-terminal trimming of the optimal epitope by the endoplasmic reticulum aminopeptidase I [7]. These results demonstrate that allele-associated sequence variation within the flanking region of CTL epitopes can alter antigen processing. Identifying such mutations is of major relevance in the construction of vaccine sequences.

**HIV-Specific CD4 T-Cell Responses Target Preferentially Gag and Nef**

Interest in HIV-specific CD4 T-cell responses has been growing over the past years. For the first time, these responses were now assessed comprehensively using overlapping peptides spanning all HIV proteins [8]. HIV-1-specific CD4 responses were identified in 30 of the 36 individuals studied, with the strongest and broadest responses detected in persons treated in acute infection who underwent treatment interruption. In individuals with identified responses, the total number of recognized HIV-1 peptides ranged from 1 to 36 (median, 7) and the total magnitude of responses ranged from 80 to > 14,600 (median, 990) spot-forming cells/10(6) CD8-depleted PBMC. Neither the total magnitude nor the number of responses correlated with viremia. The most frequent and robust responses were directed against epitopes within the Gag and Nef proteins. Peptides targeted by >/=25% of individuals were then tested for binding to a panel of common HLA-DR molecules. All bound broadly to at least four of the eight alleles tested, and two bound to all of the HLA-DR molecules studied. Fine mapping and HLA restriction of the responses against four of these peptides showed a combination of clustering of epitopes and promiscuous presentation of the same epitopes by different HLA class II alleles. These findings have implications for the design of immunotherapeutic strategies and for testing candidate HIV vaccines.

**Therapeutic Dendritic-Cell Vaccine for Simian AIDS**

In animal models, dendritic cells (DC) generated ex vivo and delivered in vivo are highly effective at inducing protective immune responses against a variety of pathogens and tumors. However, so far no one has demonstrated whether DCs can be used to increase control of immunodeficiency virus in animals or humans. Lu et al. [9] showed in simian immunodeficiency virus (SIV)-infected rhesus monkeys that effective and durable SIV-specific cellular and humoral immunity is elicited by a vaccination with chemically inactivated SIV-pulsed DC. After three immunizations given at 2-week intervals, the animals exhibited a 50-fold decrease in SIV DNA and a 1,000-fold decrease in SIV RNA in peripheral blood. Such reduced viral load levels were maintained over the remaining 34 weeks of the study. Molecular and cellular analyses of axillary and inguinal node lymphocytes of vaccinated monkeys revealed a correlation between decreased SIV DNA and RNA levels and increased SIV-specific T-cell responses. Neutralizing antibody responses were augmented and remained elevated. The authors conclude that inactivated whole virus-pulsed dendritic cell vaccines are promising means to control diseases caused by SIV/HIV.

**Rapid Viral Escape to Neutralizing Antibodies**

In view of a protective HIV vaccine, neutralizing antibodies are probably most important, but protective immunity by antibodies has been difficult to assess. This was studied recently using a new technique [10]. A recombinant virus assay was used to characterize in detail neutralizing antibody responses directed at circulating autologous HIV in plasma. Examining serial plasma specimens in a matrix format, most patients with primary HIV infection rapidly generated significant neutralizing antibody responses to early (0-39 months) autologous viruses, whereas responses to laboratory and heterologous primary strains were often lower and delayed. Plasma virus continually and rapidly evolved to escape neutralization, indicating that neutralizing antibody exerts a level of selective pressure that has been underappreciated based on earlier, less comprehensive characterizations. These data argue that neutralizing antibody responses account for the extensive variation in the envelope gene that is observed in the early months after pri-