Hot News

New Insights into the Mechanisms Driving Immune Activation in HIV

Generalized immune activation is one of the key pathogenic factors involved in the relentless $CD4^+$ depletion and progression to AIDS in HIV-infected individuals. It is now clear that the level of immune activation, measured as T-cell activation, correlates with the rate of CD4 depletion and with disease progression, and that the prognostic value of immune activation is independent of HIV replication. Indeed, immune activation represents the link between HIV replication and CD4 depletion. On the basis of this hypothesis, an important question arises: if immune activation is necessary for CD4 depletion, can we observe T-cell depletion in the absence of immune activation even in the face of active viral replication? Fortunately, we have an *in vivo* model to answer this question and the answer is "no". Natural hosts of SIV, such as sooty mangabeys and african green monkeys, do not develop CD4 depletion even though they are infected and support high levels of SIV viremia. In contrast, non-natural hosts of SIV, such as rhesus macaques, develop CD4 depletion and ultimately AIDS-defining illnesses. The difference between these two outcomes seems to depend on the level of immune activation. While in the natural host there is only limited immune activation and proliferation of $CD4^+$ T-cells, rhesus macaques show a heightened immune activation and proliferation of T-cells following SIV infection.

The next important question is: what is the link between HIV/SIV replication and immune activation? In the last few years, information has arisen linking the early and severe depletion of mucosal $CD4^+$ T-cells with immune activation and disease progression in non-natural hosts of SIV infection. According to this hypothesis, known as the microbial translocation model, severe damage of the gut-associated lymphoid tissue and depletion of the majority of resident $CD4^+$ T-cells leads to the loss of the mucosal barrier and hence to the massive influx of microbial components into the bloodstream, activating the immune system. Although this is still a hot topic in the HIV/SIV research field, a critic of the model comes from the fact that a similar degree of mucosal $CD4^+$ T cell depletion occurs in nonpathogenic SIV infection of natural hosts, in whom immune activation is lacking. Thus, it remains unclear if immune activation is the consequence, as the model proposes, or the cause of microbial translocation. In the latter situation, the mechanisms linking viral replication and immune activation still remain unsolved.

A recent study by Mandl, et al. (Nature Med. 2008;14:1077-87) has examined the early immunologic events following after acute SIV infection in a comparative experimental infection model. Sooty mangabeys and rhesus macaques were acutely infected with the same SIV_{sm} strain, and early innate immune responses were analyzed and compared between both species. The authors found host-specific differences in innate immune responses, which could represent determinants of whether or not immune activation and disease may follow AIDS virus infection. The main differences observed between both species were: (i) an increase in natural killer cell activation and proliferation in rhesus macaques; (ii) a lack of activation of plasmacytoid dendritic cells in sooty mangabeys; and (iii) very low levels of interferon alpha (IFNα) production by plasmacytoid dendritic cells in sooty mangabeys. This limited production of IFNα was specific for SIV stimulation and was mediated through toll-like receptors (TLR) 7 and 9 that are expressed by mature plasmacytoid dendritic cells. Interestingly, lymphocytes from HIV-infected individuals expressed similar amounts of mRNA for IFNα as those from rhesus macaques and much lower than those from sooty mangabeys.

The authors subsequently examined where in the signaling cascade of TLR7 and TLR9 receptors was the defect responsible for the inability of sooty mangabey plasmacytoid dendritic cells to produce large amounts of IFNα after exposure to SIV. They found several polymorphisms in the sooty mangabey's gene encoding for interferon regulatory factor 7 (IRF7), a transcription factor involved in the downstream signaling pathway after TLR7 or TLR9 engagement. These polymorphisms were not observed in rhesus macaques and human IRF7 genes.

On the basis of all these results, the authors concluded that the exacerbated IFNα response to HIV and SIV infections may be the underlying factor responsible for the generalized immune activation typically seen in HIV-infected humans and SIV-infected rhesus macaques. This observation has important clinical implications, including the potential usefulness of several immunomodulatory interventions that could ameliorate pathologic immune activation. This is the case of using TLR antagonists to halt IFNα production in response to TLR-viral engagement. Alternatively, inhibition of chronic IFNα production could be accomplished using antibodies capable of neutralizing IFNα. On the basis of this hypothesis, trials in the primate model using immunomodulatory approaches are warranted.

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HIV Vaccines: What are we Learning from Failure?

Despite extraordinary advances in understanding the genetic regulation of HIV, host restriction factors, and immune responses to the virus, the scientific community has failed so far to develop an effective vaccine for HIV. Suggestions and hope that vaccine able to induce T-cell responses could protect from disease were principally derived from studies in non-human primates. In this model, vaccination with T-cell vaccines resulted in decreased primary and chronic plasma virus levels, and when sufficient animals were studied, delayed disease progression. However, it has also become clear that protection from disease in most animals is not long lasting and eventually SIV replication resumes and causes overt AIDS.

Two recent studies have addressed the underlying reason for the failure of T-cell vaccines to protect vaccinated macaques in the long term. Collectively, these studies suggest that because vaccination with T-cell vaccines does not protect from the profound loss of CD4+ T-cells induced by SIV, effective CD8+ T-cell responses become ineffective over time. This conclusion was derived from a study (Vaccari, et al. J Virol. 2008;82:9629-38), whereby the impact of in vivo depletion of CD4+ T-cells on virus-specific CD8+ T-cell responses during immunization with DNA (in the contest of a DNA/MVA prime-boost vaccine strategy) was evaluated in macaques. During the acute phases of infection with SIVmac251, no differences were observed in plasma viral load or viral replication in the tissues between vaccinated-CD4 depleted and animals vaccinated in normal conditions. However, over time, plasma virus levels increased faster in macaques vaccinated in conditions of CD4+ T-cell deficiency. The loss of control of viral replication in these animals was associated with the presence of SIV-specific CD8+ T-cells with diminished ability to produce interleukin-2.

The implication of this study is that vaccines that do not protect from CD4+ T-cell depletion will not protect in the long term because CD8+ T-cells become ineffective. Interestingly however, early CD4+ T-cell depletion alone is not sufficient to cause AIDS as it occurs also in nonpathogenic models of SIV infection, suggesting that other events are necessary for progression to AIDS. Indeed, in a second study, vaccination had a demonstrated added benefit in as much as it also decreased the expression of markers of immune activation and immune suppression such as cytotoxic T-lymphocyte-associated antigen-4, indoleamine 2,3-dioxygenase, forkhead box protein-3, and transforming growth factor-β (Vaccari, et al. Mucosal Immunol. 2008;1:497-507). Thus, an effective vaccine for HIV should protect against both early CD4+ T-cell loss and the onset of immune activation.

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