Immune Response and HIV Infection: Old Problems for New Challenges

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Abstract — The infection with HIV, the virus that causes AIDS, triggers a number of immune responses that have the aim to control the production and propagation of the virus, mainly by blocking its binding to CD4+ T cells by neutralizing antibodies, or killing infected cells by cytotoxic T lymphocytes. However, in most cases the immune system is not able to control this retrovirus, that uses sophisticated evolutionary mechanisms to survive and propagate its progeny. In this review some immune mechanisms that try to contrast HIV are discussed, putting an accent on the variety of problems that immunologists have had, and actually have in designing and producing an effective vaccine.

Keywords — HIV infection; Immune response; HIV candidate vaccines

I. INTRODUCTION

Since the identification of HIV as the cause of AIDS, about 30 years ago [1], enormous progresses have been done in the knowledge of the natural history of the infection, in the immunopathogenesis and treatment of HIV/AIDS, and in the changes occurring in the immune system of the host. The introduction of combined antiretroviral therapy (cART) in 1995 has profoundly changed the history of HIV infection [2], allowing an efficacious suppression of viral replication, and the recovery of CD4+ T cell count in the peripheral blood to a level that assures immunocompetence. However, cART is not able to eradicate the infection, and can only partially restore the functionality of the immune system, in terms of thymic output of naïve T cells [3], bone marrow activity [4], and recovery of normal clonal distribution of T cells [5]. Worse still, the elevated cost of therapy, the strict adherence required for its success, the numerous collateral effects [6, 7], and the risk of development of viral resistances remain unsolved problems. At present, the cost of cART and the difficulty to access to hospitals for receiving treatment do not allow to implement such a cure in developing countries. Thus, an immune based approach for controlling, and hopefully preventing HIV infection is absolutely needed.

Unfortunately, we are still far from developing an effective vaccine, which is the Holy Grail of HIV research. A number of vaccine candidates have been developed in the last 25 years, but no significant success has been reported in preventing infection [8-16]. The modest protection against infection observed with the RV144 phase III trial [17] has been considered promising, even if not so strong as desired. There are several, unresolved problems that can explain, at least in part, these failures.

First, there are no documented cases of immune-mediated clearance of the virus in an infected individual. So far, only in one case a patient has been considered cured, but the eradication of the virus has been achieved not because of the action of the host’s immune system, but by means of CCR5 Δ32/Δ32 stem cells transplantation [18, 19]. Thus, an example of naturally protective immune response able to eradicate the virus is still missing, and this does not allow to identify the appropriate viral antigens useful to develop an effective vaccine.

Second, HIV-1 is characterized by an enormous variability, with differences in some coding regions higher than 40% among different genetic subtypes, by a high rate of mutations while replicating, and an apparent high tolerance to mutations. These features readily allows the virus to escape both cytotoxic response and neutralizing antibodies [20]. Moreover, they make extremely difficult to identify viral epitopes that are at the same time highly immunogenic, present in all viral quasi-species, and that could not undergo mutations without impairing virus cell cycle. So far, any possible strategy in choosing antigens for vaccine has been attempted including whole inactivated virus, subunit vaccines, DNA-based vaccines and viral vectors. None of them has lead to significant protection or improvement of host immune response.

Third, the issue of how the immune system could fight against a retroviral infection need to be clarified. Indeed, it
has to be taken into account that a large amount of human DNA derives from the integration of retroviruses in our genome, which occurred during evolution. Thus, conceptually, the immune system has to win against a mechanisms that has created diversity for millions of years.

Fourth, the control of HIV-1 infection relies on the capability of the immune system to trigger an effective response in different compartments of adaptive immunity. From this point of view, another problem to be solved remains the quality (beside the quantity) of CD4+ T cells, along with the clinical monitoring of such elements before and after antiretroviral treatment. Indeed, CD4+ T cell count only represents the sums of individual cellular subsets, and does not reflect the actual composition. Thus, it is a common fact that patients with a similar or identical CD4+ T cell count can display a different qualitative composition within this subset, and likely diverging functional characteristics [21]. For example, a high increase in Treg could paradoxically inhibit a cytotoxic immune response, giving the opposite of the desired effect. Moreover, several studies have shown that control of viral replication is associated with the capability to elicit polyfunctional responses either by CD4+ or CD8+ T cells specific for HIV antigens [22-25]. Unfortunately, this response occurs quite rarely in HIV+ patients and the reason why only a limited number of patients show this kind of specific response remains to be elucidated.

Fifth, the immune response is deeply affected by the genetic background of the host. Extensive studies have been performed to identify variants of human genes that affect the natural history of HIV infection, and the recent advent of genome wide association studies (GWAS) has greatly increase the possibility to identify new genetic polymorphisms affecting disease progression [26-30]. However, these studies have been conducted mainly in cohorts of European or European descent patients, and little is known on possible, important polymorphisms in populations where the impact of HIV infection is more relevant. To date, only a limited number of genes, namely HLA-B and C, CCR2 and CCR5 [31], have been associated with the control of the progression of HIV infection, but further studies are needed on larger and different cohorts.

Some solutions to the issues discussed above could likely be found by a deeper analysis of the immune response in selected cohort of patients such as “elite controllers”, patients during acute infection, and finally exposed, uninfected patients. Indeed, a small percentage of HIV-infected patients, referred to as “elite controllers”, are able to control HIV replication to undetectable levels, without significant reduction of CD4+ T cell count for more than 20 years [32, 33]. Such capability has been associated to the polyfunctionality of T cells [34] and a particularly effective CD8+ T cell response [35, 36]. A better understanding of this strong HIV-specific response could represent a model for identifying the compartments of the immune system that should be activated in order to gain an effective immune response in normal HIV+ patients.

Control of viral replication is associated with HLA types B*57:01, B*27:05 and B*14 [27, 37]. It can be argued that viral peptides presented by these MHC I molecules are able to evoke stronger CD8 T-cell responses and in turn allow viral control. The identification of the epitopes from HIV-1 presented by these molecules will help to design more effective vaccines.

Studies in acute HIV-1 infected patients, i.e. patients infected by less than 2-3 weeks can provide crucial information concerning the mechanisms at the basis of the initial control of viral replication, and of the influence that this first “footprint” given to immune response has in the capability to control or not the infection during the chronic phase. Specific CTL responses have been detected in almost all cases of acute HIV infection, and are associated with the reduction of the peak of the viral load and to its stabilization to the set-point reached at the end of the acute phase [38, 39]. The role of protective molecules such as neutralizing antibodies in controlling viral replication during acute infection is far from being clear [40, 41]. The main obstacle to deeper analysis of immune response during acute phase is patients’ recruitment: the large part of them are not aware of being infected by HIV, and thus do not present to infectiologists.

Finally, several cohorts of patients repeatedly exposed to HIV-1 without being infected have been identified in different countries [42, 43]; they usually belong to three categories, i.e. sex workers, discordant couples, and subjects exposed non sexually, such as haemophiliacs or drug users. It must be noted that, despite the absence of virus in these patients, exposure to HIV-1 deeply affects CD4+ T cell features, by stably changing their miRNA expression profile [44]. Thus, this finding should be taken into account for future immunological studies about CD4+ T cell dynamics during HIV infection and in response to immune based therapies, as it clearly indicates that are viral products, rather than virus per se, to cause some of the changes observed in CD4+ T cells of HIV+ patients.

References


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