HLA-associated immunodominance and responsiveness to cancer vaccines

Danila Valmori
INSERM U601, Nantes, France

Abstract

CTL responses to pathogens are generally limited to a minor fraction of the many potential antigenic determinants encoded by the corresponding genomes, a phenomenon termed immunodominance (1). Both in studies in model systems using inbred mice and in humans, immunodominance has been shown to focus the CTL response to even large viruses to a limited number of determinants often presented in the context of defined HLA class I restricting alleles. The impact of HLA class I allele-associated immunodominance on clinical outcome has been recently documented for HIV, where expression of individual HLA class I alleles restricting immunodominant CTL responses has been clearly associated with slower disease progression (2). However, only few indications of a possible association between certain HLA alleles and clinical course in cancer patients have been reported so far, and the impact of HLA allele-associated immunodominance on the development of CTL responses to full-length recombinant tumor specific antigens has not yet been explored. The non-mutated self-antigen NY-ESO-1 belongs to the group of CTA, developmental antigens frequently expressed in human tumors. Although its function remains unknown, NY-ESO-1 is one of the best characterized human tumor antigens and induces spontaneous integrated antibody and T-cell responses in cancer patients bearing antigen-expressing tumors. For these reasons, NY-ESO-1 is regarded as a model tumor antigen for the development of generic cancer vaccines. In a recent study, we have obtained evidence that immunization with a NY-ESO-1 recombinant protein emulsified with Montanide® ISA-51 and CpG ODN 7909 induces integrated antibody and CD4+ T-cell responses to NY-ESO-1 in all vaccinated patients, at an early phase of the vaccination protocol. However, only half of them also developed specific CTL responses, which often became detectable at a later time point (3). The average level of antibody responses was higher in the group of patients who developed CTL responses as compared to the group that did not, indicating a role of NY-ESO-1 specific antibodies in the cross-priming of CTL. However, some individual patients who failed to develop CTL mounted antibody responses at levels similar to those of some of the responder patients, suggesting that additional factors may impact on the ability of the patients to develop CTL following immunization with the NY-ESO-1 recombinant protein. To unveil these factors, we have assessed epitope recognition and HLA-restriction of vaccine-induced CTL from responder patients in the study. Overall, our data show that recognition of immunodominant NY-ESO-1 epitopes by the large majority of vaccine-induced CTL was restricted by few frequently expressed HLA alleles. All responder patients expressed at least one of these HLA alleles, whereas none of the non-responder patients expressed them. Together, our data show that, in this antigenic system, HLA class I alleles associated immunodominance determines the patient’s ability to develop specific CTL responses following vaccination with a full-length recombinant tumor antigen. As recombinant tumor antigens including several CTA but also differentiation and over-expressed antigens are presently among the most promising candidate cancer vaccines under assessment in both academic and industry sponsored clinical trials, we suggest that the immunological monitoring of such trials should systematically include the assessment of HLA association with responsiveness. Finally, our findings emphasize the importance of taking into account human genetic variation in the development of cancer vaccines.

References

