Identification of an HLA-A3-Restricted Cytotoxic T Lymphocyte (CTL) Epitope from ML-IAP

To the Editor:

ML-IAP (also named livin) is a critical cellular factor since increased expression levels confer resistance to apoptotic stimuli, thereby contributing to the pathogenesis and progression of melanoma (Kasof and Gomes, 2001; Nachmias et al., 2003). Thus, the majority of melanoma cell lines express high levels of ML-IAP in contrast to primary melanocytes. Additionally, Nachmias et al., recently detected the livin protein in ten of 27 melanoma cultures from primary melanoma patients. Furthermore, they demonstrated the significance of livin in the drug-resistance phenotype characterizing this disease and showed a clinical correlation between livin expression and chemotherapeutic response. Thus, the attractiveness of using ML-IAP for vaccination purposes is based on the fact that downregulation or loss of expression of this protein as some form of immune escape would impair sustained tumor growth. In this regard, we recently demonstrated that a large proportion of melanoma patients host a spontaneous T cell response specifically against ML-IAP-derived peptides presented in the context of the HLA-A2 antigen (Andersen et al., 2003).

One of the HLA-A2 antigen-restricted epitopes identified from ML-IAP was the decamer peptide ML-IAP245–254 (RLQEERTCKV). Interestingly, the analog nona-mer peptide ML-IAP245–253 (RLQEERTCK) comprises the perfect anchor motif for the HLA-A3 antigen (leucin at position 2 and lysine at C-terminal position) (Kubo et al., 1994). Since the decamer peptide is presented by melanoma cells in the context of the HLA-A2 antigen, it can be presumed that the nona-mer peptide likewise is generated by the antigen-processing machinery and subsequently is presented in the context of HLA-A3 antigen. To investigate this, we analyzed peripheral blood lymphocyte (PBL) from 14 HLA-A3 antigen-positive melanoma patients for spontaneous immune responses by means of ELISPOT against this peptide. To this end, five of the melanoma patients hosted an immune response of more than 200 ML-IAP245–253 (RLQEERTCK) specific T cells per 10^5 CD8^+ cells (Fig 1). Thus, spontaneous immune responses against this epitope are present in around one-third of the HLA-A3 antigen-positive patients. In the present study, we have only examined late-stage melanoma patients only treated by surgery. Thus, it is not possible to conclude if the presence of a CTL immune response against ML-IAP correlates with certain characteristics of the disease.

The characterization of multiple ML-IAP epitopes with different HLA class I restriction elements broadens the clinical potential of this target antigen in two important ways:

On the one hand, it increases the number of patients eligible for immunotherapy based on ML-IAP derived peptides, since even though the HLA-A2 antigen is one of the most frequently expressed HLA class I molecules, it is still only expressed in around 50% of melanoma patients. The HLA-A3 antigen is expressed by 30% of patients (Kessler et al., 2003). Co-expression is found in around 10% of patients. Thus, approximately 70% of the patients can be vaccinated with the ML-IAP epitopes identified thus far. This percentage of patients would be further increased by the identification of additional ML-IAP peptide epitopes that is restricted to other common HLA class I alleles such as HLA-A1, HLA-A11, and HLA-A24 antigens. The combination of these would encompass >90% of the Caucasian population (Vonderheide et al., 2001).
One the other hand, the collective targeting of several restriction elements is likely to decrease the risk of immune escape by class I HLA-allele loss. Loss of a single class I HLA allele is a significant component of MHC alterations described in cancer cells, whereas total loss of class I HLA expression is a rather infrequent event (Garrido et al., 1997; Koopman et al., 2000; Marincola et al., 2000). Although the percentage of patients expressing both HLA-A2 and HLA-A3 antigens is only 10%, the identification of epitopes for other class I HLA alleles will increase this percentage of patients with allelic overlap.

Over the past decade, numerous clinical trials have shown the feasibility of peptide specific vaccination to induce anti-tumor T cell responses in cancer patients. The clinical course of the patients, however, was in most cases not improved. This discrepancy has in numerous cases been explained by immune escape mechanisms of the tumor cells (Campoli et al., 2002). The attractiveness of using ML-IAP for vaccination purposes relies on the fact that downregulation or loss of expression of this protein as a means of immune escape would impair sustained tumor growth. The availability of multiple ML-IAP epitopes presented by different HLA class I restriction elements further reduces the risk of immune escape and thereby therapeutic failures. It should be mentioned, however, that use of the gene products of one HLA class I locus as restricting elements does not counteract downregulation of the gene products of one locus as an escape mechanism. The use of peptides using gene products of different HLA class I loci as restricting elements may be more effective.

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References