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High frequency of functionally active Melan-A specific T cells in a patient with progressive immunoproteasome-deficient melanoma

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Tumor-reactive T cells play an important role in cancer immuno-surveillance. Applying the multimer technology, we report here an unexpected high frequency of Melan-A-specific CTL in a melanoma patient with progressive lymph node (LN) metastases, consisting of 18% and 12.8% of total peripheral blood and tumor-infiltrating $CD8^+$ T cells, respectively. Melan-A-specific CTL revealed a high cytotoxic activity against allogeneic Melan-A-expressing target cells but failed to kill the autologous tumor cells. Loading of the tumor cells with Melan-A peptide reversed the resistance to killing, suggesting impaired function of the MHC class I Ag processing and presentation pathway. Mutations and/or down-regulation of the MHC class I heavy chain, the antigenic peptide TAP, and tapasin could be excluded. However, RT-PCR and immunohistochemical analysis revealed a deficiency of the immunoproteasomes low molecular weight protein (LMP)2 and LMP7 in the primary tumor cells, that affects the quantity and quality of generated T cell epitopes and might explain the resistance to killing. Overall, this is the first report of an extremely high frequency of tumor-specific CTL that exhibit competent T cell effector functions, but fail to lyse the autologous tumor cells. Immunotherapeutic approaches should not only focus on the induction of a robust anti-tumor immune response, but also have to target tumor immune escape mechanisms.