

Possible mechanisms of tumor regression after vaccination with MAGE antigens

Pierre G. Coulie*, Christophe Lurquin, Bernard Lethé, Nicolas van Baren, and Thierry Boon

Institute of Cellular Pathology and Ludwig Institute for Cancer Research, University of Louvain, Brussels, Belgium

*Presenting author

Following vaccination of metastatic melanoma patients with MAGE antigens, we have observed some evidence of tumor regression in about 20% of the patients. Even in these responding patients, the anti-vaccine cytolytic T-cell (CTL) response was almost always either undetectable or present at a frequency below 10^{-5} of CD8 T cells, a frequency which might be deemed too low to enable these CTL to produce tumor rejection on their own. We therefore examined the possibility that T cells recognizing other tumor antigens might participate in the tumor regression process. As a first step, we evaluated in 5 patients the blood frequencies of anti-tumor CTL, i.e. lytic effectors that recognized the autologous melanoma cells but not autologous B cells nor NK target K562. After vaccination, frequencies of anti-tumor CTL in the blood ranged from 10^{-4} to 3×10^{-3} of the CD8 T cells, that is 10 to 10,000 times higher than the anti-vaccine CTL in the same patient. Surprisingly, high frequencies of circulating anti-tumor CTL were also observed in these five patients before vaccination.

From a patient who had shown nearly complete tumor regression following vaccination against a MAGE-3 antigen presented by HLA-A1, we derived 15 anti-tumor CTL clones. Ten recognized antigens encoded by the cancer-germline gene *MAGE-C2*, and 3 recognized antigens encoded by melanocyte differentiation gene *gp100*. High frequencies of circulating anti-tumor CTL were also observed before vaccination, including CTL recognizing MAGE-C2 and gp100 antigens. Our results indicate that when metastatic melanoma patients receive a vaccine, they have already made a high spontaneous response against the types of tumor antigens that are often used for vaccination. At that time, the anti-tumor T cells are clearly ineffective in halting tumor progression, but if vaccination somehow results in their activation, their high number may enable them to be the main effectors of tumor rejection.

To evaluate the potential contribution of the anti-tumor T cells to the tumor rejections that occurred following vaccination, we measured the frequency of the anti-vaccine and anti-tumor T cells inside metastases of the patient mentioned above. The frequency of anti-MAGE-3.A1 T cells was 2.5×10^{-6} of CD8 T cells in the blood and it was 6-fold higher in an invaded lymph node. An anti-tumor CTL clone recognizing an antigen encoded by MAGE-C2 showed a considerably higher enrichment. Whereas in the blood the frequency of this CTL was 9×10^{-5} , it was about 1,000 times higher in the invaded lymph node. Several other anti-tumor T cell clonotypes also had frequencies above 1% and appeared to constitute the majority of the T cells present in this site. Similar findings were made on a regressing cutaneous metastasis.

These results suggest that the anti-vaccine CTL may not be the principal effectors that kill the bulk of the tumor cells. They may exert their effect mainly by an interaction with the tumor that

creates conditions enabling the stimulation of large numbers of CTL directed against other tumor antigens, which then proceed to destroy the tumor cells. New naive T cells may be stimulated in the course of this process, as we observed that new anti-tumor CTL clonotypes emerged following vaccination and were present in the metastases at a very high frequency. An implication of this wide T-cell response triggered by the vaccine is that loss of the vaccine antigen by a number of tumor cells would not ensure tumor escape.

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