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Melanoma, immune surveillance, and immunotherapy.

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Research Article

Editorial

The recent progress in cellular immunology and recombinant DNA technology has facilitated the acquisition of tools to evaluate the validity and efficacy of immunotherapy for malignant diseases. Interest in these investigations, in turn, has stimulated the characterization of tumor-associated antigens expressed by malignant cells, as well as that of the molecular basis of the recognition of malignant cells by the host's immune system. These two lines of research have been especially explored in human malignant melanoma, since several lines of evidence suggest that the immune system plays an important role in the pathogenesis and in the clinical course of the disease. First, it has been known for some time that patients with malignant melanoma may develop a cellular and/or humoral immune response to melanoma associated antigens (MAA) expressed by autologous tumor cells. Second, the presence in patients' sera of antibodies to glycolipids or glycoproteins expressed by melanoma cells, whether spontaneously formed or induced by active specific immunotherapy, appears to have a beneficial effect on the clinical course of the disease (1, 2). Third, adoptive transfer of tumor-infiltrating lymphocytes (TIL) and interleukin-2 can result in the regression of metastatic lesions in selected patients with advanced melanoma (3). Last, spontaneous regressions occur more frequently in malignant melanoma than in other types of malignancies.

The possibility that regressions are caused by the host's immune response to MAA is suggested by the tumor infiltration with lymphocytes. The latter are often in close contact with regressing nests of melanoma cells. However, no functional data were available to document that such an immune response takes place in regressive lesions. This evidence is provided in this issue of *The Journal* (4) and in recently published papers by Mackensen et al. They take advantage of the PCR technology to analyze the variability of T cell receptor (TCR) β chains expressed by lymphocytes infiltrating a regressive melanoma lesion. The authors show selection and expansion of clonal T cell populations at the tumor site with a predominance of T cells expressing the Vβ16 variable gene segment, thereby providing evidence that antigen-driven T cell selection may occur at the tumor site.

In vitro expansion of TIL resulted in the overgrowth of T cell clones that are underrepresented in-vivo, however, did not generate any Vβ16$^+$ T cell lines. The lack of in vitro proliferation of Vβ16$^+$ T cells, in spite of their preponderance in the regressive melanoma lesion analyzed, is intriguing. Do T cells with a clinically relevant cytotoxic activity not grow in vitro because of the lack of crucial cytokine(s) in the culture medium? Does the close contact between TIL and melanoma cells in a regressive lesion reflect the secretion of the required cytokine(s) by melanoma cells? Does the limited efficacy of immunotherapy with the currently used cytokines reflect their inability to stimulate cytotoxic T cells with a clinically relevant cytotoxic activity? Last, does the analysis of the specificity as well as of the characteristics of cytotoxic T cell lines and clones, generated in vitro from TIL, provide clinically relevant information? Answers to these questions may not only define the differential cytokine requirements of functionally distinct T cell subpopulations present in melanoma lesions, but may also contribute to the optimization of the use of cytokines in the therapy of malignant diseases.

By using an anti-Vβ16 TCR mAb to select for the corresponding cells from TIL and to trigger their in vitro proliferation, Mackensen et al. (4) succeeded in generating a Vβ16$^+$ T cell line that is cytotoxic for autologous melanoma cells. What makes this cell line so interesting and distinct from the many previously published T cell lines and clones with cytotoxic activity for autologous melanoma cells? The cytotoxic Vβ16$^+$ T cell line, described by Mackensen et al. (4), was derived from a metastatic lesion where immunosurveillance mechanisms appear to have been successful in controlling melanoma cell growth. Previously, T cell lines attributed with cytotoxic activity for melanoma cells had been derived mainly from patients whose immune systems failed to control the disease. Therefore, comparison of the specificity and functional characteristics of the Vβ16$^+$ T cell line to those of the previously described T cell lines is expected to contribute to the identity of variables that determine the successful control and elimination of tumor cells by the host's immune system.

The Vβ16$^+$ T cell line was found to lyse autologous melanoma cells in an HLA class I–restricted fashion. Testing with a limited panel of target cells suggests a restricted tissue distribution of the antigen recognized by the Vβ16$^+$ T cell line, since the latter did not lyse autologous lymphoid cells. Furthermore, the Vβ16$^+$ T cell line did not lyse two allogeneic melanoma cell lines. Whether the latter finding reflects the recognition by the Vβ16$^+$ T cell line of a private MAA and/or the lack of expression of the HLA class I–restricting element by the two allogeneic melanoma cell lines tested is not known, since the HLA phenotype of the two allogeneic melanoma cells lines is not reported and the antigen recognized by the Vβ16$^+$ T cell line has not been identified yet. Hopefully, characterization of the target antigen and of its tissue distribution will be described in future publications, since it may have an impact on designing immunotherapeutic approaches to melanoma. Specifically, identification of the antigen(s) recognized by the Vβ16$^+$ T cell line will shed some light on the nature of target structures that a patient's immune system can successfully use for in vivo lysis of melanoma cells. Furthermore, analysis of the tissue distribution of the antigen recognized by the Vβ16$^+$ T cell line will advance our understanding of the variables that restrict the cytotoxic activity of T cells recognizing MAA to melanoma lesions. This information, in turn, may improve the selection of MAA for immunotherapy of melanoma.

The cytotoxicity of the Vβ16$^+$ T cell line, like that of many previously described T cell lines and clones generated by in vitro expansion of TIL and peripheral blood lymphocytes of patients with melanoma (5), is HLA class I restricted. While the restricting element of the Vβ16$^+$ T cell line is an HLA-B allospecificity, the restricting element of most of the previously described cytotoxic T cells originated from patients with progressive disease is a gene product of the HLA-A locus. The functional significance of this difference and its effect on the selection of the MAA used as a target remain to be determined. Irrespective of the results of these investigations, the HLA class

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I restriction of the cytotoxicity of T cells for melanoma cells implies that the latter may take advantage of structural and/or functional abnormalities in HLA class I antigens to escape from immune recognition. In this context, a recent review of the literature (6) has shown that HLA class I antigens are not detectable in about 20% of primary and 40% of metastatic melanoma lesions. Furthermore, selective loss of an HLA class I allospecificity may occur in about 20% of melanoma lesions without detectable abnormalities in their staining by mAbs recognizing framework determinants of HLA class I antigens (7). Lastly, defects in peptide processing and transport have also been described in malignant cells (8). Identification of the molecular mechanisms underlying structural and functional abnormalities in HLA class I antigens expressed by melanoma cells will suggest approaches to correct these defects. These approaches will have to be combined with vaccines to avoid having the potential benefits of immunotherapy for melanoma undermined by the resistance to T cell–mediated cytotoxicity that melanoma cells acquire because of abnormalities in HLA class I antigen expression.

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