Can We Define the Mechanism of Antitumor Response Observed During Clinical Adoptive Immunotherapy?

Recent reports (1,2) have raised interest in the use of immunization with tumor cell vaccines to treat melanoma and renal cell carcinoma (RCC). Such vaccines can be used to generate specific T cells from draining lymph nodes (1,3). Chang et al. (1) have shown the feasibility of activating and expanding these cells ex vivo to large numbers over a short interval and some efficacy of these cells after reinjection into the patients.

Nevertheless, the mechanism of antitumor response during adoptive immunotherapy is unclear. We (4) previously reported the results of a gene-marking study of tumor-infiltrating lymphocytes (TILs) in patients with melanoma or RCC. In that study, we demonstrated long-term survival of cells after reinjection but no selective homing at tumor sites. Economou et al. (5) confirmed those results.

More recently, delayed-type hypersensitivity (DTH) to autologous tumor cells served as a qualitative measurement of T-cell response in a dose-escalation trial with granulocyte-macrophage colony-stimulating factor (GM-CSF)-transduced autologous RCC cells (6). Important DTH reactivity was noted at the highest dose levels, and a partial response (at least 50% reduction in all measurable lesions) was observed in a patient who displayed the largest DTH conversion; in biopsy specimens, cellular infiltration with mononuclear cells and perivascular cuffing by lymphocytes were observed. Although the T-cell repertoire has not been precisely analyzed, this reaction has been interpreted as a qualitative assessment of the T-cell response to GM-CSF gene-transduced vaccine.

Thus, in one patient with metastatic RCC treated with NeoR gene-marked TILs, we performed an autologous tumor cell skin test to investigate local cellular response and, notably, the vaccine site migration of reinjected cells. TILs were essentially CD8+ T cells with cytotoxic activity against the autologous tumor and clonal T-cell expansion, as defined by the restriction of the T-cell receptor β-chain repertoire, which suggests a response to potential tumor antigens (7). The patient received a high number of NeoR gene-marked TILs that were detected on day 90 in the blood but not in a transcutaneous liver metastasis biopsy specimen. Irradiated autologous tumor cells admixed with bacille Calmette-Guérin were used to vaccinate intradermally (8) the patient on day 15 after reinjection of TILs. An important DTH reaction with induration and erythoderma was observed at the injection sites, but biopsies failed to reveal the presence of marked TILs, although they were concomitantly detectable in the circulation. This result argues against a selective attraction of adoptively transferred TILs in the tumor. A critical re-appraisal of the role of TILs in adoptive immunotherapy is necessary because their use was based on their preferential homing at tumor sites and an efficacy dependent on their specific cytolytic activity.

Taken together, these results outline the need for biologic tools to accurately define the mechanism of antitumor response during adoptive immunotherapy. Gene labeling of cells offers an interesting tool to address directly biologic questions such as the in vivo trafficking of immunocompetent cells after reinjection. The measurement of DTH responses by use of dissociated autologous tumor cells appears useful in the evaluation of the specific immune response, but molecular analyses of the T-cell repertoire in biopsy specimens is required to establish whether an association exists between tumor regression induced by immunotherapy and oligoclonal T-cell population expansion (7).

References


Notes

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