Helping Tumor Cells To Die

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Urine tumor model systems first developed in the 1950s demonstrated that adoptively transferred cells, but not serum, from mice that had been immunized with irradiated tumor cells could mediate regression of established tumor lesions. Some of the first studies to demonstrate that adoptively transferred T lymphocytes isolated from mice that had been immunized with irradiated tumor cells were effective at mediating the regression of established tumor lesions were carried out in the laboratory of Alexander Fefer, the senior author of the Pillars of Immunology article highlighted in this issue of *The Journal of Immunology* and a pioneer in the field of tumor immunology. The injection of relatively large doses of FBL-3 leukemia cells (0.5–1 × 10⁷ cells) led to disseminated tumors that could not be treated with sensitized T cells alone; however, durable tumor regressions were observed in mice that received cyclophosphamide before the adoptive transfer of sensitized T cells, but not chemotherapy or T cells alone (1). The effects of chemotherapy appeared to be due, at least in part, to transient reductions in the levels of endogenous T suppressor cells that attenuated the responses of transferred effector T cells (2, 3). The increased availability of homeostatic cytokines (4, 5), along with the release of innate immune activators (6) observed after cytoreductive preparative regimens, has subsequently been found to play a significant role in enhancing the survival and function of adoptively transferred T cells. These observations, along with findings made in cancer trials using transplantation of allogeneic bone marrow or peripheral blood stem cells (7), have served as the basis for preparative regimens used in many of the recent and ongoing T cell cancer adoptive immunotherapy trials.

The current *Pillars of Immunology* article was focused on identifying the primary effector T cell population from immunized mice that was responsible for mediating FBL-3 tumor regression (8). Although the median survival of untreated tumor-bearing mice in this set of experiments was 19 d, 70% of mice that received spleen cells from immunized mice after cyclophosphamide treatment survived more than the 80 d observation period. Surprisingly, 50% of mice that received Lyt1+2− (CD4+) T cells survived for 80 d, whereas only 17% of mice receiving Lyt1−2+ (CD8+) cytolytic T cells survived for 80 d. The ability of spleen cells from immunized mice to lyse FBL-3 target cells in vitro appeared to be reduced, but not completely eliminated, by treatment with anti–Lyt-2 Ab plus complement, which was used to prepare the Lyt1+2− T cells, whereas treatment with anti–Lyt-1 Ab, which was used to prepare the Lyt1−2+ T cells, appeared to result in a modest reduction in their lytic capacity. Results presented in a subsequent report from this group excluded a role for host CD8+ T cells in the treatment of FBL-3 leukemia-bearing mice with immune CD4+ T cells (9). Subsequent observations have clearly demonstrated that many tumor Ag–reactive CD4+ T cells are capable of directly lysing tumor target cells. These findings raised the possibility that tumor elimination involved the direct lysis of class II+ FBL-3 cells by immune CD4+ T cells; however, FBL-3 tumor cells are class II negative and cannot be induced by IFN-γ to express class II molecules, implying that indirect tumoricidal mechanisms were being engaged.

Studies carried out with T cells isolated from TCR transgenic mice have provided the means to more clearly evaluate the ability of CD4+ as well as CD8+ tumor-reactive T cells to mediate tumor regression. Transgenic CD4+ T cells expressing a class II–restricted TCR recognizing an epitope of the male H-Y Ag have been found to be effective in treating mice bearing class II–negative male tumors (10), and TCR transgenic T cells recognizing a mutated class II–restricted epitope of the L9 protein (mL9) were found to mediate the regression of mL9 protein–expressing class II–negative fibrosarcomas (11). Adoptively transferred tumor-reactive TCR transgenic CD8+ T cells were also effective in treating mice bearing Ag loss variant tumors (12, 13) and class I mismatched tumors (14). These results indicate that the recognition of peptides or peptide–MHC complexes released from tumor cells presented on endogenous APCs can lead to tumor regression. The ability of T cells that are unable to recognize tumor cells directly to mediate tumor regression may result from their ability to damage supportive stromal tissue (12–14). The ability of activated effector T cells to release IFN-γ, as well as host cells to respond to IFN-γ, has also been found to be a critical component of these responses (12, 14). These findings raise the possibility that alteration and/or destruction of tumor stroma could represent a common mechanism responsible for the elimination of tumors initiated by effective tumor-reactive T cells, although further characterization of the cell types involved in this process is needed to fully establish its importance for tumor regression.

It is difficult to assess the relevance of murine model systems that involve treatment of tumors that have been established for only days or weeks prior to T cell transfer to the treatment of patients bearing long-established tumors. Currently, however, only limited data are available to assess the role of adoptively transferred CD4+ tumor-reactive T cells in mediating...
tumor regression in cancer patients. Although a complete regression of metastatic lesions was observed in a melanoma patient who received an autologous CD4+ T cell clone directed against an HLA class II–restricted epitope of the NY-ESO-1 Ag (15), tumor regressions were not observed in eight additional patients who received autologous CD4+ T cell clones that recognized the same epitope. Durable complete tumor regressions have been observed in significant percentages of patients with advanced B cell leukemias and lymphomas who were treated with bulk populations of PBMCs that were transduced with a chimeric Ag receptor directed against the cell-surface CD19 molecule (16, 17), as well as metastatic melanoma patients treated with bulk populations of tumor-infiltrating lymphocytes that contained variable percentages of CD4+ T cells after in vitro expansion (18–20). Although bulk populations of CD8-enriched, tumor-infiltrating lymphocytes containing, on average, 3–4% CD4+ T cells after in vitro expansion were also effective at mediating tumor regression in some patients (21), it is difficult to draw firm conclusions regarding the contribution of individual cell types to tumor regression, given the fact that a relatively small number of cells could play a significant role in these responses. However, this Pillars of Immunology report by Greenberg et al. provided the first demonstration that class II–restricted tumor Ag–reactive T cells can be effective in mediating the complete regression of established tumor lesions. This represents an important principle that has been validated in a variety of additional tumor model systems, demonstrating the direct and indirect means by which CD4+ T cells can contribute to tumor eradication, and will hopefully lead to the development of more effective cancer therapies.

Disclosures
The author has no financial conflicts of interest.

References