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COMMENTARY

Tumor stromal barriers to the success of adoptive T cell therapy

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Adoptive transfer of tumor competent T cells has long been studied as a therapeutic modality that may result in complete tumor eradication [1]. Indeed, T cells have the potential to home to all sites of metastatic disease no matter where the location and induce antigen-specific cell destruction. Theoretically, local clonal expansion of T cells in response to antigen will allow persistent killing over time until every cancer cell has been eradicated. No chemotherapeutic or biologic therapy developed to date has the ability to result in a persistent long lived anti-tumor effect. Unfortunately, the road to developing successful adoptive T cell therapy as a standard treatment for solid tumors has been littered with roadblocks.

Barriers to success have included difficulty in expanding T cells ex vivo to the number needed to elicit an anti-tumor effect, a need to better define the specific effector populations mediating tumor regression, and a lack of consensus as to the appropriate origin of the T cells to be used for expansion, i.e. derived from tumor, lymph nodes, or peripheral blood, to name a few [2]. Moreover, the development of T regulatory cells (Treg) [3], co-expanded ex vivo with activated T cells, can dampen the function of tumor-specific T cells and prevent effective in vivo expansion, thereby limiting anti-tumor responses [4]. Investigations have also focused on the optimization of the effector T cell to enhance tumor homing and clinical efficacy [5–7]. In this issue of *Cancer Immunology and Immunotherapy*, however, Bernhard et al. [8] elegantly demonstrate that functional effectors, capable of homing to antigen, encounter further barriers at the site of the tumor. A detailed analysis of an infused HER-2/neu specific $CD8^+$ T cell clone, in a patient with breast cancer, suggests that tumor stromal factors [9] may be preventing egress of T cells into malignant parenchyma.

Following ex vivo expansion and infusion into patients, T cells must retain anti-tumor activity, survive and persist, and localize to all tumor sites [10]. T cells that lack these properties are destined to have limited anti-tumor efficacy in vivo. Efforts to improve anti-tumor activity by optimizing specificity include the introduction of defined T cell receptor chains or chimeric antigen receptors to generate high-avidity tumor-reactive T cells [7]. Delivery of survival signals can be mediated via restoration of costimulatory signals and co-administration of growth cytokines, such as IL-2 [5]. Furthermore, T cell homing to tumors can be improved through use of tissue-specific chemokine receptors, such as CCL21 [11]. Despite optimizing the T cell product, it is clear that failure can occur due to the tumor microenvironment. Cancer immunoediting can arise, i.e. the host's immune system can facilitate outgrowth of tumor cell variants that downregulate or lose antigen [12] and MHC class I and II, thereby decreasing the immunogenicity of the tumor [13]. Therefore, while an adaptive immune response can be induced by antigen-specific T cells, cancer immune surveillance is often inadequate at controlling carcinogenesis and disease progression. Furthermore, within the tumor microenvironment, tumor-derived and Treg-derived cytokines, such as IL-10 and TGF-β, can facilitate

Commentary on "Adoptive transfer of autologous, HER2-specific, cytotoxic T lymphocytes for the treatment of HER2-overexpressing breast cancer" by Helga Bernhard et al.

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escape from immune attack by inducing immune suppression and allowing tumor progression and metastasis [2].

The data presented by Bernhard et al. indicate that it is clearly not enough that T cells home to tumor, they must extravasate and infiltrate the tumor bed. The ability to penetrate tumor is critical. In colorectal cancer, the correlation of intratumoral T cells with favorable prognosis has been observed; those tumors with a high density of effector memory T cells were associated with greater disease-free and overall survival than those without T cells [14]. Moreover, the composition and density, along with location of the immune cells within the tumors, were found to be stronger predictors of patient survival than current histopathological staging methods [15]. Earlier studies in ovarian cancer demonstrated the presence of intratumoral T cells is highly correlated with improved clinical outcome [16]. In advanced stage ovarian cancer, patients whose tumors contained intratumoral T cells had a significantly higher five-year overall survival than those whose tumors did not (38 versus 4.5%, respectively).

Given the importance of lymphocytic infiltration into tumors, the study by Bernhard's group raises an important question. How can the tumor stroma be pertubated clinically to enhance T cell egress? Induction of thermal stress might be the key to improved lymphocytic entry into tumors. It has been suggested that febrile temperatures provide a 'danger signal', which mobilizes and enhances entry of lymphocytes, via L-selectin, across high endothelial venules (HEV). Recently, Chen et al., using mice treated with whole-body hyperthermia (WBH) to mimic physiological fever, demonstrated thermal stress upregulated ICAM-1 and CCL21 expression on HEV, which contributed to enhanced lymphocyte trafficking, and that the process was regulated by IL-6 [17]. Extending these observations to a tumor model, B16-ova mice receiving WBH prior to adoptive T cell transfer of $CD8^+$ OT-1 lymphocytes had a statistically significant reduction in tumor growth compared to normothermal control mice [18]. Other potential adjuncts to T cell transfer include irradiation and chemotherapy. The rationale for combination therapy is that if one treats tumors, which express low levels of antigen with local irradiation or a chemotherapeutic agent, greater release of antigen should be facilitated, subsequently sensitizing the tumor stroma for killing by CTL [19]. Tumors are eradicated and antigen variants are unable to grow out [12]. These are just a few of the novel strategies being evaluated. Undoubtedly, combination approaches of adoptive T cell therapy with agents that disrupt tumor stroma are necessary for therapeutic success.

Although there are significant challenges to the clinical translation of adoptive T cell therapy, it must be remembered that there have also been significant successes. Most notable is the use of donor lymphocyte infusions (DLI) for the treatment of hematological malignancies, such as chronic myeloid leukemia (CML), that have relapsed post allogeneic hematopoietic stem cell transplantation [20]. For CML, complete remissions in chronic phase have been observed in 70–80% of treated patients and responses are often seen even months after the end of treatment. Recently, it was reported that transfer of EBV-reactive T cells could control advanced stage EBV^+ Hodgkin's disease, which was otherwise resistant to conventional therapies [21]. Bernhard et al., here, provide compelling evidence that HER-2/neu reactive CTL are capable of clearing metastatic HER-2/neu^+ tumor cells from the bone marrow. Thus, solid tumor antigens can be effectively targeted by adoptive T cell therapy at certain sites.

Identifying mechanisms of failure will lead to solutions that ensure success. The work by Bernhard and her colleagues offers hope that breast cancer cells can be eradicated by antigen-specific T cells and clearly delineates the importance of tumor penetration by T cells to achieve therapeutic efficacy. Such work lays the foundation for the development of combination modalities to enhance the therapeutic efficacy of adoptive T cell therapy with a focus both on the effector cell as well as the environment.

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