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Meeting Abstract

Adoptive immunotherapy for cancer: Building on success

Nicholas P. Restifo

National Cancer Institute, NIH, Bethesda, MD, USA

Abstract

Substantial progress has been made in our understanding of the molecular and cellular bases of T cell mediated anti-tumor responses. T cells are potent effectors of the adaptive anti-tumor immune response. Some target antigens recognized by tumor-reactive CD8+ T cells are non-mutated self-antigens that are also expressed by tumor cells. The molecular signals that modulate T-cell activation, function and memory are being elucidated. Both positive and negative signals from co-stimulatory molecules have been shown to shape the anti-tumor response. Cytokines, including those with receptors that contain the common cytokine-receptor gamma chain have been shown to alter the programming of effector CD8+ T cells.

Therapeutic cancer vaccines, designed to activate the anti-tumor immune response *in vivo* are still under development. Adoptive cell transfer (ACT) therapies activate T cells *ex vivo* prior to the transfer back to patients. Preclinical studies have indicated that immune ablation is an effective preconditioning regimen that can increase T-cell responses after adoptive transfer. Adoptive transfer of anti-tumor T cell after non-myeloablative but lymphodepleting systemic chemotherapy can induce clear and reproducible responses in a substantial percentage (~50%) of treated patients who have multivisceral, bulky melanoma that is refractory to standard treatments including chemotherapy, radiation and cytokine therapies.

The specific mechanisms that contribute to the impact of a lymphodepleting preconditioning regimen are now being elucidated. Although it seems counter-intuitive that the efficacy of ACT-based tumor immunotherapy can be improved by the removal of the host immune system, several mechanisms might underlie the augmented efficacy of tumor-reactive T cells in the lymphopenic environment. These factors include the elimination of immunosuppressive cells such as CD4+CD25+ regulatory T (Treg) cells, the depletion of endogenous cells that compete for activating cytokines and the increased function and availability of antigen-presenting cells (APCs) due to the activation of Toll-like receptors, specifically the engagement of TLR4 that results from bacterial translocation.

Emerging findings from both mouse studies and clinical trials indicate that intrinsic properties related to the differentiation state of the adoptively transferred T cell populations are critical to the success of ACT-based approaches. CD8+ T cell subsets in both mice and humans are characterized by a progressive pathway of CD8+ T cell differentiation. Mouse models indicate that CD8+ T cells that acquired terminal effector properties have increased anti-tumor activity *in vitro* but are less effective at triggering tumor regression *in vivo*. Less differentiated, central memory-like T cells might proliferate and become fully activated in the lymphopenic environment, which is rife with homeostatic cytokines such as IL-7 and IL-15. Evidence in humans indicates that the expression of CD27 and long telomeres by adoptively transferred T cells are associated with clinical effectiveness. Findings in mice emphasize that early effector T cells are more effective than late effector T cells. In humans, standard rapid expansion protocols that employ CD3-specific antibody and high doses of IL-2 with irradiated allogeneic feeder cell may result in the differentiation of tumor-specific CD8+ T cells to an intermediate and late effector state.

Cytokines, acting in concert with signals through the TCR and co-stimulatory molecules, can function as accelerators or brakes for T cell proliferation and differentiation. IL-2 has been shown to be an effective T cell growth factor but has undesirable effects including the ability to decrease the expression of lymph node homing molecules and promote the terminal differentiation of T cells, predisposing them to activation-induced cell death. Other cytokines with a receptor that contains γc such as IL-7, IL-15 and IL-21 may be useful *in vitro* and *in vivo* as support for the activation or proliferation of tumor-reactive CD8+ T cell populations for ACT.

Tumor-specific T cells can be generated by genetically engineering mature peripheral blood T cells in mouse and in man. The affinity of the TCR selected for transduction, the level of transduced TCR expressed on the cell surface and the differentiation state of the transduced T cells used for ACT might critically contribute to the success of trials following TCR transduction. Naturally occurring T cells expressing high affinity TCRs specific for self/tumor antigens might be difficult to obtain owing to intra-thymic deletion, however generation of high affinity TCRs can be performed *in vivo* in immunized HLA-A2 transgenic mice or *in vitro* by phage display of TCRs containing degenerate complementarity-determining regions.

Integration of retrovirally-delivered sequences requires active division of target cells, a process that also promotes T-cell differentiation but lentiviral vectors are less dependent upon active cell division and might be used to transduce high-affinity TCRs into T cells without driving differentiation. Delivery of both the alpha and beta chains of the TCR directs expression of the intact TCR, however, pairing with endogenous TCR alpha and beta chains can occur, thereby reducing the surface density of tumor-specific TCR.

Genes other than TCR have been proposed for transduction of tumor-reactive T cells in order to improve their quality and functionality, including co-stimulatory molecules, anti-apoptotic molecules, pro-inflammatory or homeostatic cytokines and chemokine receptors. Transduction with genes encoding TCRs specific for known epitopes allows the concurrent employment of vaccines in order to enhance the anti-tumor response of adoptively transferred T cells. Most importantly, the genetic modification of anti-tumor T cells makes it possible for immunotherapies to treat virtually any cancer histology.