CANCER IMMUNOTHERAPY

Establishment of Antitumor Memory in Humans Using in Vitro–Educated CD8$^+$ T Cells

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Although advanced-stage melanoma patients have a median survival of less than a year, adoptive T cell therapy can induce durable clinical responses in some patients. Successful adoptive T cell therapy to treat cancer requires engraftment of antitumor T lymphocytes that not only retain specificity and function in vivo but also display an intrinsic capacity to survive. To date, adoptively transferred antitumor CD8$^+$ T lymphocytes (CTLs) have had limited life spans unless the host has been manipulated. To generate CTLs that have an intrinsic capacity to persist in vivo, we developed a human artificial antigen-presenting cell system that can educate antitumor CTLs to acquire both a central memory and an effector memory phenotype as well as the capacity to survive in culture for prolonged periods of time. We examined whether antitumor CTLs generated using this system could function and persist in patients. We showed that MART1-specific CTLs, educated and expanded using our artificial antigen-presenting cell system, could survive for prolonged periods in advanced-stage melanoma patients without previous conditioning or cytokine treatment. Moreover, these CTLs trafficked to the tumor, mediated biological and clinical responses, and established antitumor immunologic memory. Therefore, this approach may broaden the availability of adoptive cell therapy to patients both alone and in combination with other therapeutic modalities.

INTRODUCTION

The diagnosis of melanoma with distant metastases carries a median survival of less than 1 year (*1*). However, recent clinical trials suggest that adoptive T cell therapy can induce long-lasting clinical responses and may prolong overall survival (*2*). Successful adoptive T cell immunotherapy necessitates the generation of tumor-specific T lymphocytes that have the capacity to eliminate or control the growth of cancer cells (*3*–*8*). Investigators have developed strategies to isolate and expand large numbers of CD8$^+$ T lymphocytes (CTLs) that exhibit both antitumor specificity and effector function. Although these CTLs have been adoptively transferred to cancer patients without significant toxicity, biological and clinical activity were limited in early studies (*9*–*12*). Considerable evidence suggests that one of the mechanisms limiting their efficacy is the failure of these CTLs to persist in vivo (*3*, *10*, *13*–*15*).

To address the failure of CTLs to persist when adoptively transferred, investigators have developed strategies to expand engrafted CTLs in vivo. Administration of interleukin-2 (IL-2) after adoptive T cell transfer significantly increases both T cell survival and biological activity (*10*, *12*, *16*, *17*). Preinfusion lymphodepletion using myeloablative therapy combined with IL-2 administration further improves persistence of engrafted antitumor T cells and, moreover, has been associated with durable clinical responses (*2*, *13*, *18*). Lymphodepletion is thought to increase access to homeostatic cytokines such as IL-7 and IL-15, eliminate suppressive regulatory T cells, and provide T cells space to expand (*2*, *18*–*21*).

We have developed an alternative strategy to overcome the failure of adoptively transferred CTLs to persist that requires the generation of antitumor CTLs with a central memory and an effector memory phenotype and an intrinsic capacity to survive. Previously, we reported the development of a human cell–based artificial antigen-presenting cell (aAPC) genetically engineered to express HLA-A*0201 (A2), CD80, and CD83. These aAPCs expanded large numbers of CTLs restricted to various tumor-associated antigens in vitro from peripheral CD8$^+$ T cells in the presence of IL-2/IL-15 (*22*, *23*). These antigen-specific CTLs demonstrated a central memory and an effector memory phenotype and were remarkably long-lived in vitro, persisting more than a year without allogeneic feeder cells or cloning (*23*).

Here, we tested whether these unique antitumor CTLs generated with gene-engineered aAPC and IL-2/IL-15 could persist in humans. MART1-specific CTLs were generated in vitro from melanoma patients and then infused back without lymphodepletion or IL-2 administration. We chose the melanoma-associated antigen MART1 as our target because necessary immune assessment technologies to evaluate persistence and localization of infused MART1 T cells are widely available (*10*, *12*). We report that CTLs with a memory phenotype generated using the aAPC-based system could be safely infused and functioned as memory T cells; these cells persisted long term, trafficked to tumors, and induced antitumor biological and clinical responses in humans.

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