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γδ T Cells: A New Frontier for Immunotherapy?

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ABSTRACT

The use of cytolytic effector cells as therapy for malignant disease has been a central focus of basic and clinical research for nearly 2 decades. Since the original descriptions of in vitro lymphocyte-mediated cytotoxicity against human tumor cells, there have been numerous attempts to exploit such observations for therapeutic use, with decidedly mixed results. Most studies have focused on the role of either natural killer cells or cytotoxic CD8$^+$ αβ T cells as the primary mediators of antitumor cytotoxicity, and until recently little attention has been paid to the role of γδ T cells in this capacity. This is partially due to a lack of understanding of the mechanisms of γδ T-cell immune responses to tumors, as well as the practical problem of obtaining a sufficient number of γδ T cells for clinical-scale administration. In this article, we discuss the biological and clinical rationale for developing γδ T cell–based immunotherapies for the treatment of a variety of malignant conditions. It is our view that infusing supraphysiological numbers of tumor-reactive γδ T cells—either in the autologous or allogeneic setting—might be used to restore or augment innate immune responses against malignancies. Accordingly, we will also discuss how we and others are working to overcome some of the practical limitations that have so far limited the direct clinical delivery of highly purified human γδ T cells for the treatment of both hematologic and solid tumors.

KEY WORDS

γδ T cells • Immunotherapy • Cell therapy • Innate immunity

INTRODUCTION

The transfer of cytolytic effector cells into tumor-bearing hosts with the intent to eradicate disease has been the focus of a great deal of basic and clinical research for nearly 2 decades [1-13]. Since the original descriptions of lymphocyte-mediated cytotoxicity against human tumor cells in vitro, there have been numerous attempts to exploit such observations for therapeutic use in humans, with decidedly mixed results [5,14-16]. Clinical applications of adoptive cellular immunotherapy have included the treatment of patients with various malignancies (such as melanoma) by using interleukin (IL)–2–stimulated lymphokine-activated killer cells derived from autologous peripheral blood. Similarly, tumor-infiltrating lymphocytes, first isolated from primary tumors and subsequently cultured and expanded ex vivo, have also been administered clinically. Although historically a great deal of emphasis has been placed on the role of either natural killer (NK) cells or cytotoxic CD8$^+$ αβ$^+$ T cells as the primary mediators of antitumor cytotoxicity [17-24], until now little attention has been paid to the role of human γδ T cells in this capacity.

γδ T CELLS FORM PART OF THE INNATE IMMUNE DEFENSE AND ARE POTENT ANTITUMOR EFFECTORS

Whereas most mature T cells express the αβ T-cell receptor (TCR) heterodimer, a small proportion express an alternative γδ TCR heterodimer [25-28]. Unlike αβ T cells, which recognize specific processed peptide antigens presented on major histocompatibility complex (MHC) molecules by antigen-presenting cells, γδ T cells seem to directly recognize and respond to a variety of MHC-like stress-induced self-antigens expressed by malignant

cells [29-33]. Thus, γδ T cells can recognize malignant cells through less specific mechanisms that require no prior antigen exposure or priming, a function that is shared by other innate immune cells such as macrophages and NK cells [25]. Although γδ T cells comprise <10% of total peripheral blood T cells, they are present in substantially greater numbers within epithelial tissues such as skin, intestine, and lung [34-37], contrasting with αβ T cells, most of which either circulate in the peripheral blood or are resident in lymphoid organs.

The process by which γδ T cells recognize stressed or malignant cells is not completely understood. Although the TCR is involved in antigen recognition [38], the mechanism by which antigens are recognized by γδ T cells is fundamentally different from that for both αβ T cells and NK cells [25,39]. Although a detailed discussion on the biology of γδ T-cell recognition and the shaping of the γδ T-cell repertoire is beyond the scope of this article (several excellent reviews on this subject are available [39-42]), it is important to note that both genetic and extrinsic factors, such as environmental antigens, likely play a key role in shaping the γδ T-cell repertoire.

Several lines of evidence point to a role for γδ T cells in tumor immunosurveillance. It has recently been shown that mice lacking γδ T cells are highly susceptible to multiple regimens of cutaneous carcinogenesis [29]. In clinical studies, γδ T cells have been shown to infiltrate a variety of tumors, including lung cancer [43,44], renal cell carcinoma [45], seminoma [46], and breast cancer [47]. The most common circulating γδ T cells, ie, those expressing the Vγ9/Vδ2 TCR heterodimer (sometimes designated Vγ2Vδ2, because Vγ9 forms part of the Vγ2 gene family) [48], recognize several known tumor-associated ligands and cell lines. These include HSP-60 [49,50], Daudi Burkitt lymphoma [51,52], and glial cells [52]. Vγ9/Vδ2 γδ T cells recognize and lyse glioblastoma [53], neuroblastoma [54], multiple myeloma [55], and lung cancer [56]. CD30-restricted Vγ9Vδ2$^+$ T cells have been isolated from patients with Hodgkin disease [57], and Vγ9/Vδ2 T cells recognize cells with increased mevalonate metabolites, which are overexpressed in hematologic malignancies and mammary carcinoma cells [58].

Vδ1$^+$ T cells are less frequent, comprising up to 10% of all γδ T cells. They seem to recognize a different set of ligands and tumors, although there is some overlap with Vδ2$^+$ cells. A high proportion of Vδ1$^+$ γδ T cells appear in epithelial tumors from lung, breast, kidney, ovary, prostate, and colon that express the stress-induced antigens MICA and MICB [59], a nonclassic stress-related MHC antigen recognized by Vδ1$^+$ cells [60]. Primary leukemias are also are killed by γδ T cells. Duval et al. [61] showed that γδ T cells isolated from patients with leukemia expanded in IL-2–containing cultures to a greater degree than γδ T cells isolated from healthy controls. Vδ1$^+$ and Vδ2$^+$ T cells both expanded, and the Vδ1$^+$ clones lysed the acute lymphoblastic leukemia (ALL) cell line NALM-6. Lamb et al. [62] later showed that Vδ1$^+$ T cells proliferated when cultured with primary acute leukemia cells and became cytotoxic to the primary leukemia but did not lyse normal lymphocytes. In addition, Vδ1$^+$ γδ T cells seem to recognize Epstein-Barr virus–transformed B cells [63], primary blasts obtained from patients with acute myeloid leukemia acute myeloid leukemia [64] and B-cell ALL [61], and lung cancer–derived cell lines [65]. However, the means by which γδ T cells recognize these targets are not yet understood.

SEVERAL PROPERTIES OF HUMAN γδ T CELLS MAKE THEM PARTICULARLY SUITABLE FOR INTENSIVE STUDY IN THE SETTING OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

A number of in vitro and in vivo studies suggest that γδ T cells might be ideally suited for study specifically in the context of hematopoietic stem cell transplantation (HSCT). First, γδ T cells can mediate innate antitumor activity. Second, evidence suggests that γδ T cells might be capable of facilitating allogeneic engraftment. Moreover, it seems that γδ T cells likely to do not initiate graft-versus-host disease (GVHD). Despite these intriguing findings, however, few studies specifically address the role of γδ T cells in the setting of clinical HSCT.

Association between Allogeneic Graft γδ T-Cell Content and Disease-Free Survival

The first indication that γδ T cells might protect against disease relapse in bone marrow transplantation (BMT) patients was reported by Lamb et al. [66] in a study of patients undergoing allogeneic HSCT for ALL or AML. In this report, it was noted that several patients who received bone marrow grafts depleted of αβ T cells subsequently developed spontaneous increases in γδ T-cell numbers during the first year after HSCT. These patients were found to have a significant improvement in disease-free survival (DFS) when compared with similar-risk patients. It is interesting to note that the absolute increase in γδ T cells persisted in surviving patients for up to several years after transplantation. In a follow-up study, it was determined that a post-BMT absolute increase in γδ T cells was significantly associated with αβ T-cell depletion, because patients who received grafts that were T-cell depleted with OKT3, a pan T-cell monoclonal antibody, rarely showed an increase in γδ T cells after BMT (P = .05) [67]. Finally, Godder et al. [68] recently showed that the improved DFS of patients with increased γδ T cells is sustained over several years (Figure 1).