The T-body approach: potential for cancer immunotherapy


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Introduction

The immune system, with its exquisite specificity and potent effector mechanisms, has been suggested as an ideal tool for tumor therapy. Both the humoral and cell-mediated arms of the immune system have the ability to recognize foreign or tumor antigens via surface immunoglobulin or T cell receptor (TCR) binding. Moreover, both have the ability to eliminate the target cell by antibody recruitment of complement-mediated cytotoxicity or antibody-dependent cell-mediated cytotoxicity on the one hand, or by T cell-mediated cytolysis on the other. Nevertheless, neither humoral immunity nor cell-mediated immune responses have proved to be sufficiently effective in tumor therapy.

Cancer patients generally do not mount an effective immune response against their own tumors. Most spontaneous tumors escape the immune system because they are not sufficiently immunogenic or antigenic. Some, while potentially immunogenic, are able to evade or suppress a specific host-mediated immune response. Thus, most immunotherapeutic approaches attempt to provide the patient with either active or passive immunity directed against a particular tumor antigen. In this article we shall review a new approach, which we have recently developed, combining the humoral and cellular arms of the immune system to convey passive immunity against tumor cells. This technology (which we have named “T-bodies”) makes use of cytotoxic immune effector cells transfected with a chimeric receptor of antibody-type specificity. These cells maintain their effector function, which is redirected to tumor cells by a receptor that recognizes antigen in the absence of MHC determinants.

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Our rationale in developing this technology stemmed from the many experimental and clinical studies which demonstrated difficulties in conventional immunotherapy. While anti-tumor antibodies, used alone or linked to a toxin, drug, or radioisotope, are effective against some tumors [26], antibodies penetrate large tumors poorly [18] and are therefore ineffective against most solid tumors, especially in advanced disease. Cytotoxic T cells are better able to home to and target a tumor site, are quite effective in penetrating tumors, and their cytotoxic effector mechanism is highly efficient and specific. Unfortunately, tumor-specific T cells are rare, and have been found only in several melanoma and renal cell carcinoma patients.

Our group [8, 9, 11-13] and others [3, 10, 19] have combined the humoral and cellular arms of the immune system to create the T-body approach. Using recombinant DNA technology, an antibody-derived variable (V) region of the desired specificity is grafted onto the TCR constant regions or onto a T cell signalling molecule of choice. This construct is then introduced into an effector (cytotoxic) cell population, thereby redirecting these cells to an antibody-determined specificity. Since the recognition element is derived from an antibody variable region, the redirected T cells are MHC independent and are not individual specific. We will describe here the basic construction and possible configurations of T-bodies, review results from some of our early studies using anti-hapten systems, and outline the progress that has been made towards adapting this approach to tumor immunotherapy.

**The T-body concept: basic configurations**

In our early studies [11-13, 20], we used a two-chain configuration (Fig. 1) which required the transfection of two constructs into the effector T cell of choice. In this configuration, the constant (C) region of each of the two (α and β) chains of the TCR is linked to an immunoglobulin heavy or light chain variable region (VH or VL) derived from an antibody of the desired specificity. The resulting chimeric receptor genes containing CαVL and CβVH, (or CαVH and CβVL) are then transfected into the effector T cell population. For surface expression and signal transduction the chimeric TCR (cTCR) heterodimers must associate with the CD3 complex. All the early studies with two-chain receptors utilized anti-hapten antibodies [3, 10-12, 19]. We transduced cytotoxic T cell hybridoma lines with trinitrophenyl (TNP)-specific chimeric receptor genes and showed specific secretion of interleukin-2 (IL-2) and cytolysis of hapten-modified target cells in response to antigen. Besides establishing the feasibility of the T-body approach, these experiments with hapten-specific receptors allowed the definition of some of the properties of chimeric TCR of this sort. Studies with haptens [13] showed that both VH and VL can be combined with either Cα or Cβ of the TCR. A single chimeric chain can associate with the complementary endogenous TCR to form a heterodimeric receptor. For many anti-hapten antibodies, most of the binding energy is contributed by the VH chain. In such cases, a chimeric receptor chain containing the VH can pair with the endogenous complementary TCR chain to yield a functional receptor with anti-hapten specificity. The cTCR could endow the T cell with non-MHC-restricted or -dependent antibody-type specificity, and in fact serves as the formal proof that MHC restriction is confined to the V region of the TCR. Transgenic mice have also been produced containing a VH Cα chimeric receptor chain [3]. This receptor associates in vivo with the native TCRβ chain, producing a functional receptor.