Abstract

Introduction

Cellular therapies including γδ T cells, NK–92 cells, and cytokine–induced killer (CIK) cells have shown modest anti–tumor activity against multiple hematological and solid malignancies in preclinical and phase I/II clinical trials. We investigate whether the antitumor activity of these cellular therapies can be augmented by using a novel method that rapidly affixes tumor–targeting antibodies directly to cell surface proteins.

Methods

Monoclonal antibodies including rituximab and daratumumab were conjugated to the cell surface proteins using a three step approach. First, we conjugate single–stranded DNAs (ssDNAs) to the therapeutic monoclonal antibodies, as previously described (ref below). Next, we conjugate complementary ssDNAs to surface proteins of cells being used for cellular therapy. Finally, the
modified antibodies are attached to the modified cells via hybridization of the complementary DNA strands.

Results

We demonstrate that multiple anti-neoplastic monoclonal antibodies including rituximab and daratumumab can be conjugated to the surface proteins on a variety of cells including γδ T cells, NK−92 cells, CIK cells, and primary human T cells. Then we evaluated the killing activity of these conjugated cells in vitro, in vivo, and ex vivo. In vitro, Rituximab−armed γδ T cells and NK−92 cells demonstrated increased cytokine production (IFN−γ and granzyme B) and enhanced cytotoxic killing against multiple human B−cell non−Hodgkin lymphoma (NHL) and multiple myeloma cell lines. Similar enhanced anti−tumor activity was seen with rituximab−armed or daratumumab−armed CIK cells, as well as increased CD107a expression (a marker of cytotoxicity activity) by the antibody−armed CIK cells. Rituximab−armed primary T cells also show enhanced cytotoxic killing against Raji cells, although not as pronounced as autologous rituximab−armed CIK cells. We next evaluated the therapeutic potential of antibody−armed cell therapies in vivo in a disseminated xenograft mouse model using SCID−beige mice. Rituximab−armed γδ T cells exhibited potent anti−lymphoma activity against Raji cells, which lead to improved overall survival; whereas unarmed γδ T cells alone or with rituximab co−infusion demonstrated limited anti−lymphoma activity. We also evaluated the therapeutic activity of antibody−armed cell therapies against a primary lymphoma target ex vivo. Rituximab−arm CIK cells demonstrated enhanced cytolytic activity against primary follicular lymphoma freshly collected from a patient via fine needle aspiration biopsy.

Discussion

We have demonstrated a novel approach to create tumor−specific cellular immunotherapies without the need for genetic engineering. The antibody to cell conjugation method is straightforward. The modified antibodies can be made and stored until needed. It takes approximately 1 hour to attaching these modified antibodies to the cell surface and is performed in standard aqueous buffers, such as phosphate−buffered saline (PBS). This method is also flexible being able to conjugate multiple different antibodies to the surface proteins of a variety of different cell types. We also see enhanced cell killing across multiple hematological targets using multiple cell populations including γδ T cells, NK−92 cells, CIK cells, and primary human T cells. Overall, our data demonstrate existing monoclonal antibodies can be used to "antibody program" cell therapies for the treatment of hematological malignancies.

Ref

Disclosures Hsiao: Acepodia, Inc: Employment.

• Asterisk with author names denotes non-ASH members.

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Potential Articles of Interest

Enhanced killing of human B-cell lymphoma targets by combined use of cytokine-induced killer cell (CIK) cultures and anti-CD20 antibodies.
Alice Pievani et al., Blood

Genetically Engineered Pluripotent Cell-Derived Natural Killer Cell Therapy Provides Enhanced Antibody Dependent Cellular Cytotoxicity Against Hematologic Malignancies and Solid Tumors in Combination with Monoclonal Antibody Therapy
Huang Zhu et al., Blood

The IL-15 Superagonist ALT-803 Enhances NK Cell ADCC and in Vivo Clearance of B Cell Lymphomas Directed By an Anti-CD20 Monoclonal Antibody
Maximilian Rosario et al., Blood

Variable Contribution of Different Monoclonal Antibodies to NK Cell-Mediated ADCC Against Primary CLL Cells.
James Weitzman et al., Blood

Lenalidomide Strongly Enhances Natural Killer (NK) Cell Mediated Antibody-Dependent Cellular Cytotoxicity (ADCC) of Rituximab Treated Non-Hodkin’s Lymphoma Cell Lines In Vitro.
Lei Wu et al., Blood

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