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Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia

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To develop a therapy for drug-resistant B-lineage acute lymphoblastic leukemia (ALL), we transduced T lymphocytes with anti-CD19 chimeric receptors, consisting of an anti-CD19 single-chain variable domain (reactive with most ALL cases), the hinge and transmembrane domains of CD8α, and the signaling domain of CD3ζ. We compared the antileukemic activity mediated by a novel receptor ('anti-CD19-BB-ζ') containing the signaling domain of 4-1BB (CD137; a crucial molecule for T-cell antitumor activity) to that of a receptor lacking costimulatory molecules. Retroviral transduction produced efficient and durable receptor expression in human T cells. Lymphocytes expressing anti-CD19-BB-ζ receptors exerted powerful and specific cytotoxicity against ALL cells, which was superior to that of lymphocytes with receptors lacking 4-1BB. Anti-CD19-BB-ζ lymphocytes were remarkably effective in cocultures with bone marrow mesenchymal cells, and against leukemic cells from patients with drug-resistant ALL: as few as 1% anti-CD19-BB-ζ-transduced T cells eliminated most ALL cells within 5 days. These cells also expanded and produced interleukin-2 in response to ALL cells at much higher rates than those of lymphocytes expressing equivalent receptors lacking 4-1BB. We conclude that anti-CD19 chimeric receptors containing 4-1BB are a powerful new tool for T-cell therapy of B-lineage ALL and other CD19^{+} B-lymphoid malignancies.
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Introduction

In approximately 20% of children and 65% of adults with acute lymphoblastic leukemia (ALL), drug-resistant leukemic cells survive intensive chemotherapy and cause disease recurrence.[1,2] For patients with recurrent disease or with certain adverse disease features, such as B-lineage ALL with the t(9;22)(q34;q11), hypodiploidy <45 chromosomes, or *MLL* gene rearrangements in infants, current chemotherapy regimens are mostly ineffective.[3] Significant improvements in cure rates require the development of treatments that bypass cellular mechanisms of drug resistance and that have high therapeutic indexes.

Clinical observations suggest that T lymphocytes can control the recurrence of chemotherapy-refractory leukemia. For example, T-cell-mediated graft-versus-host disease (GvHD) is associated with delay or suppression of leukemia relapse after allogeneic stem cell transplantation.[4–6] Infusions of donor lymphocytes can have antileukemic effects,[7–10] but they carry the risk of severe GvHD and their antileukemic effect is often inadequate in ALL.[8,11,12]

T-lymphocyte specificity can be redirected by the transduction of artificial immune receptors, which typically consist of an extracellular antibody-derived single-chain variable domain (scFv) and an intracellular signal transduction molecule (eg, CD3ζ).[13–15] Allogeneic or autologous T lymphocytes expressing these receptors can be activated by cell surface epitopes targeted by the scFv and kill the epitope-presenting cells. In ALL, CD19 is an attractive target because it is expressed on virtually all leukemic cells in around 85% of cases (ie, B-lineage ALL), it is not expressed by normal nonhematopoietic tissues, and among hematopoietic cells, it is only expressed by B-lineage lymphoid cells.[16–19] However, CD3ζ signaling may not be sufficient to produce a durable immune response; without a second signal, or costimulus, T cells rapidly undergo apoptosis after stimulation.[19–22] This is a central issue for T-cell therapy of ALL because ALL cells generally lack the ligands of CD28,[23] and of 4-1BB (C Imai, D Campana, unpublished observations), the two major T-cell costimulatory molecules.

In this study, we compared the function of human T cells expressing an anti-CD19-CD3ζ receptor to that of T cells expressing a novel chimeric receptor that contains the signal transduction domain of 4-1BB (CD137) as well as anti-CD19 scFv and CD3ζ (anti-CD19-BB-ζ). 4-1BB, a tumor necrosis factor-receptor family member, was selected because it prevents activation-induced death of T cells,[24–27] induces expansion of CD8^{+} cells,[28] and enhances CD8^{+} T-cell responses during viral infection and allograft rejection.[28–31] Most importantly, extensive experimental evidence with animal models of cancer points to a crucial role of 4-1BB signaling for effective antitumor responses.[32–36] We found that anti-CD19-BB-ζ-transduced T cells have powerful antileukemic activity: they can destroy CD19^{+} ALL cell lines and primary leukemic cells at low effector: target (E:T) ratios and under conditions that approximate the *in vivo* microenvironment where leukemic cells grow.

Materials and methods

Cells

The human B-lineage ALL cell lines OP-1 [t(9;22)(q34;q11)/*BCR-ABL*],[37] and RS4;11 [t(4;11) (q21;q23)/*MLL-AF4*],[38] the T-cell lines Jurkat[39] and CEM-C7,[40] and the myeloid cell lines K562[41] and U-937[42] were available in our laboratory. Cells were maintained in RPMI-1640 (Gibco, Grand Island, NY, USA) with 10% fetal calf serum (FCS; BioWhittaker, Walkersville, MD, USA) and antibiotics. Human adenocarcinoma HeLa cells and embryonic kidney fibroblast 293T cells were maintained in

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Primary leukemia cells were obtained from patients with newly diagnosed B-lineage ALL with the approval of the St Jude Children's Research Hospital Institutional Review Board and with appropriate informed consent. The diagnosis of B-lineage ALL was unequivocal; in each case, more than 95% of leukemic cells were positive for CD19. Peripheral blood samples were obtained from healthy adult donors. Mononuclear cells were collected from the samples by centrifugation on a Lymphoprep density step (Nycomed, Oslo, Norway) and were washed two times in phosphate-buffered saline (PBS) and once in AIM-V medium (Gibco).

Plasmids

The plasmid encoding anti-CD19 scFv was previously reported.[43] The pMSCV-IRES-GFP, pEQPAM3(-E), and pRDF were obtained from the St Jude Vector Development and Production Shared Resource. Signal peptide, hinge and transmembrane domain of CD8α, and intracellular domains of 4-1BB, CD3ζ, and CD19 were subcloned by PCR using a human spleen cDNA library (from Dr G Neale, St Jude Children's Research Hospital) as a template (Figure 1). We used splicing by overlapping extension by PCR (SOE-PCR) to assemble several genetic fragments.[44] The sequence of each genetic fragment was confirmed by direct sequencing. The expression cassettes were subcloned into *Eco*RI and *Xho*I sites of MSCV-IRES-GFP vector

To transduce CD19-negative K562 cells with CD19, we constructed an MSCV-IRES-DsRed vector. The IRES and DsRed sequences were subcloned from MSCV-IRES-GFP and pDsRedN1 (Clontech, Palo Alto, CA, USA), respectively, and assembled by SOE-PCR. The IRES-DsRed cassette was digested and ligated into *Xho*I and *Not*I sites of MSCV-IRES-GFP. The expression cassette for CD19 was subsequently ligated into *Eco*RI and *Xho*I sites of MSCV-IRES-DsRed vector.

Virus production and gene transduction

To generate RD114-pseudotyped retrovirus, we used calcium phosphate DNA precipitation to transfect 3×10^6 293T cells, maintained in 10-cm tissue culture dishes (Falcon, Becton Dickinson, Franklin Lakes, NJ, USA) for 24 h, with 8 μg of one of the vectors, anti-CD19-ζ, anti-CD19-BB-ζ, or anti-CD19-truncated, 8 μg of pEQ-PAM3(-E), and 4 μg of pRDF. After 24 h, the medium was replaced with RPMI-1640 with 10% FCS and antibiotics. Conditioned medium containing retrovirus was harvested 48 and 72 h after transfection, immediately frozen in dry ice, and stored at −80°C until use. HeLa cells were used to titrate virus concentration.

Peripheral blood mononuclear cells were incubated in a tissue culture dish for 2 h to remove adherent cells. Nonadherent cells were collected and prestimulated for 48 h with 7 μg/ml PHA-M (Sigma, St Louis, MO, USA) and 200 IU/ml human IL-2 (National Cancer Institute BRB Preclinical Repository, Rockville, MD, USA) in RPMI-1640 and 10% FCS. Cells were then transduced as follows. A 14-ml polypropylene centrifuge tube (Falcon) was coated with 0.5 ml of human fibronectin (Sigma) diluted to 100 μg/ml for 2 h at room temperature and then incubated with 2% bovine serum albumin (Sigma) for 30 min. Prestimulated cells (2×10^5) were resuspended in the fibronectin-coated tube in 2–3 ml of virus-conditioned medium with polybrene (4 μg/ml; Sigma) and centrifuged at 2400 g for 2 h. The multiplicity of infection (4–8) was identical in each experiment comparing the activity of different chimeric receptors. After centrifugation, cells were left undisturbed for 24 h in a humidified incubator at 37°C, 5% CO_2. The transduction procedure was repeated on two successive days. Cells were then washed twice with RPMI-1640 and maintained in RPMI-1640, 10% FCS, and 200 IU/ml of IL-2 until use.

A similar procedure was used to express chimeric receptors in Jurkat cells, except that cells were not prestimulated. K562 cells expressing CD19 were created by resuspending 2×10^5 K562 cells in 3 ml of MSCV-CD19-IRES-DsRed virus medium with 4 μg/ml polybrene in a fibronectin-coated tube; the tube was centrifuged at 2400 g for 2 h and left undisturbed in an incubator for 24 h. Control cells were transduced with the vector only. These procedures were repeated on 3 successive days. After confirming CD19 and DsRed expression, cells were subjected to single-cell sorting with a fluorescence-activated cell sorter (MoFlo, Cytomation, Fort Collins, CO, USA). The clones that showed the highest expression of DsRed and CD19 and of DsRed alone were selected for further experiments.

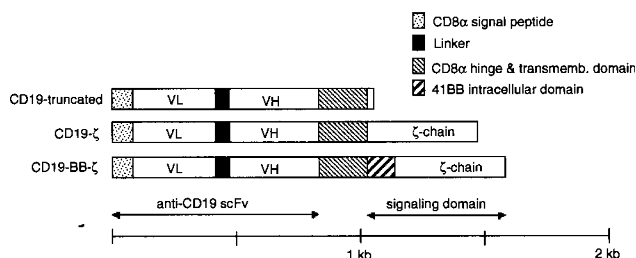
Detection of chimeric receptor expression

Cells were stained with goat anti-mouse $(Fab)_2$ polyclonal antibody conjugated with biotin (Jackson Immunoresearch, West Grove, PA, USA) followed by streptavidin conjugated to peridinin chlorophyll protein (PerCP; Becton Dickinson, San Jose, CA, USA). Anti-CD4 and anti-CD28 antibodies conjugated to PE and anti-CD8 conjugated to PerCP (from Becton Dickinson, and Pharmingen, San Diego, CA, USA) were also used. Antibody staining was detected with a FACScan flow cytometer (Becton Dickinson).

For Western blotting, 2×10^7 cells were lysed in 1 ml RIPA buffer (PBS, 1% Triton-X 100, 0.5% sodium deoxycholate, 0.1% SDS) containing 3 μg/ml of pepstatin, 3 μg/ml of leupeptin, 1 mM of PMSF, 2 mM of EDTA, and 5 μg/ml of aprotinin. Cell lysates were separated by SDS-PAGE on a 12% acrylamide gel (BioRad, Hercules, CA, USA). After transfer to a PVDF membrane, this was incubated with a mouse anti-human CD3ζ (clone 8D3; Pharmingen) and then with a goat anti-mouse IgG horseradish peroxidase-conjugated antibody. Antibody binding was revealed by using the ECL kit (Pharmacia, Piscataway, NJ, USA).

Expansion of receptor-transduced primary T cells and IL-2 production

Receptor-transduced lymphocytes (3×10^5) were cocultured with 1.5×10^5 irradiated OP-1 cells in RPMI-1640 with 10% FCS with or without exogenous IL-2. Cells were pulsed weekly with irradiated target cells at an E:T ratio of 2:1. Viable cells



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