Persuading Natural Killer Cells to Eliminate Bad B Cells

Commentary on Altvater et al., p. 4857

Laurence J.N. Cooper

Clinical trials are underway infusing T cells genetically modified to be specific for B-cell malignancies using a chimeric antigen receptor (CAR) to redirect specificity for CD19. However, issues remain about whether the CAR can provide a fully competent application signal and whether other lymphocytes with lytic capacity can target CD19+ tumors.

In this issue of Clinical Cancer Research, Altvater and colleagues investigate whether a CD19-specific chimeric antigen receptor (CAR; or chimeric receptor, chRec) can be generated to improve the ability of natural killer (NK) cells to target the CD19 molecule on the cell surface of malignant B cells, such as acute lymphoblastic leukemia (ALL; ref. 1). NK cells are an attractive cellular platform for combining gene therapy with immune-based therapy as they have endogenous cytolytic potential. This lytic potential can be clinically harnessed by adoptively transferring haplotype-mismatched (haploidentical) NK cells that are capable of lysing acute myeloid leukemia (AML) blasts (2). The killing efficiently occurs upon mismatch between killer-cell immunoglobulin-like receptors (KIR) and their ligands found on classical human leukocyte-antigen (HLA) B and C allele groups, and has been exploited to improve the graft-versus-leukemia (GVL)-effect after haploidentical hematopoietic stem-cell transplantation (HSCT), wherein engrafted allogeneic NK cells are attributed to target recipient AML blasts that lack KIR ligands (inhibiting HLA class I molecules), but present on the donor-derived NK cells (“missing ligand”; ref. 3). If engrafted haploidentical NK cells after HSCT are associated with anti-AML effect, what if haploidentical NK cells were infused without HSCT? This has been tested and shown to be effective in some patients with refractory AML when haploidentical NK cells were infused without HSCT (4). We are building upon this success to infuse haploidentical NK cells for patients with solid tumors, such as neuroblastoma (ClinicalTrials.gov Identifier: NCT00698009). However, the clinical experience with NK cells targeting AML and CML has not been duplicated for adult B-cell (B-ALL).

Rather than relying on the balance between endogenous activating and inhibitory receptors on NK cells to trigger cytolyis of tumor cells, such as B-ALL blasts, investigators have genetically manipulated NK cells to express CARs to redirect specificity for CD19. CARs are typically derived from a scFv region of a monoclonal antibody directly recognizing cell surface molecules, for example CD19. The prototypical CAR fuses the scFv exodomain with one or more intracellular chimeric signaling motifs to directly recognize tumor antigen, independent of HLA (5). Because much of the original work using CARs (aptly named “T-body,” ref. 6) was redirecting the specificity of T cells, the endodomains have been tailored for T-cell signaling. For example, a “first generation” CAR that signals solely through CD3-ζ via its three immunoreceptor tyrosine-based activation motifs (ITAMs), has been coupled in subsequent generations to CD28, 4-1BB, and other costimulatory signaling cytoplasmic domains (Fig. 1; refs. 7, 8). As the ability of CARs to redirect specificity are evaluated in populations of lymphocytes other than T cells, it is probable that the nature of the cell to be manipulated will have to be considered to develop a CAR that is a fully functional molecule capable of activating genetically modified cells for cytolsis, cytokine production and proliferation. Previously, a CD19-specific CAR was shown to activate NK cells through chimeric CD3-ζ and this signaling could be enhanced by the addition of a chimeric 4-1BB co-stimulatory endodomain (9). This work has now been expanded upon by Altvater and colleagues who generated a second-generation CAR (Fig. 1) to improve NK-cell signaling by modifying their CD19-specific CAR endodomain to include a variant of the signaling lymphocyte activation molecule (SLAM)-related receptor 2B4 (CD244), which improves CAR-dependent activation of ex vivo-propagated NK cells in response to docking with CD19. The cell-surface molecule 2B4, which recognizes CD48, is endogenously expressed on NK cells, including this group’s NK cells that have been numerically expanded ex vivo on K562-derived artificial antigen presenting cells. The endogenous 2B4 co-receptor was capable of activating NK cells that express a first-generation CD19-specific CAR when targeting a CD19â€”CD48+ leukemia cell line. To coordinate signaling through CD3-ζ and 2B4 to target primary B-ALL blasts independent of CD48 expression, a next-generation CAR was built that signals through full-length 2B4 cytoplasmic...
domain fused to CD3-ζ (designated CD19-2B4ζ). By understanding that some of the 2B4 signaling domain’s four immunoreceptor tyrosine-based switch motifs (ITSMs) may contribute to deleterious signaling, the CD19-specific CAR was further modified to include a truncated 2B4 endodomain, shortened to just signal through the first two ITSMs, and fused to CD3-ζ (designated CD19-12B4).

Just as autologous CAR+ T cells are currently being evaluated in clinical trials, preclinical data are being assembled to adoptively transfer NK cells expressing first and second generation CARs, which combine CD28 and CD3-ζ endodomains with chimeric CD137 (4-1BB), as well as other costimulatory domains. The CARs are derived from the following references: A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z.

References


Disclosure of Potential Conflicts of Interest

L. Cooper, employee, In Cellerate.
Persuading Natural Killer Cells to Eliminate Bad B Cells

Laurence J.N. Cooper


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-09-0966

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2009/09/03/1078-0432.CCR-09-0966.DC1

Cited articles
This article cites 11 articles, 8 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/15/15/4790.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/15/15/4790.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.