AIDS PATIENT CARE and STDs
Volume 30, Number 12, 2016

DOI: 10.1089/apc.2016.0226

ORIGINAL RESEARCH

Combining Cell and Gene Therapy in an Effort to Eradicate HIV

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Abstract

More than 30 million people are infected with HIV, and HIV remains the fifth leading cause of disability-adjusted life years worldwide. Antiretroviral therapy (ART) dramatically decreases mortality rate, but there are side effects, long-term toxicities, expenses, stigmas, and inconveniences associated with chronic treatment, and HIV-infected individuals on ART have an increased risk of malignancies, cardiovascular disease, neurologic disease, and shortened life expectancy. Therefore, a cure for HIV remains an important goal. Combining new cell and gene therapy technology is an exciting approach that appears promising *in vitro*. Animal testing and careful clinical trials will be needed to determine if these strategies are clinically useful.

Keywords: CCR5, cell therapy, chimeric antigen receptor, gene therapy, HIV

Introduction

More than 30 million people are infected with HIV,[1] and HIV remains the fifth leading cause of disability-adjusted life years worldwide.[2] Antiretroviral therapy (ART) dramatically decreases mortality rate,[3] but there are side effects, long-term toxicities, expenses, stigmas, and inconveniences associated with chronic treatment, and HIV-infected individuals on ART have an increased risk of malignancies,[4] cardiovascular disease,[5] neurologic disease,[6] and shortened life expectancy.[7] Therefore, developing new HIV treatment strategies that induce long-term remission or complete eradication of HIV remains an important goal.

Long Half-life and Proliferation of HIV-Infected Cells Require New Therapies That Eradicate HIV-Infected Cells

Current antiretrovirals inhibit viral enzymes, stop viral replication, and effectively reduce plasma viral load by several logs. However, HIV-infected cells are thought to have a long half-life, on the order of 3–4 years.[8,9] In addition, it has become clear that HIV-infected cells also proliferate during ART.[10–13] Although many cells are infected with defective viruses, and many proviruses never reactivate, the combination of long-lived HIV-infected cells that can also proliferate makes it unrealistic that prolonged antiretrovirals alone will cure HIV simply by allowing the reservoir of HIV-infected cells to decay. Instead, new therapeutic strategies that can kill HIV-infected cells are needed. This therapeutic challenge is similar to the challenge of treating cancer. Unlike antiviral therapy, chemotherapy is designed to kill human cells with specific properties, and therefore, it seems logical to adapt therapies that have proven promising for cancer and adapt them in an effort to cure HIV. One exciting new technology is adoptive transfer of chimeric antigen receptor (CAR) expressing T cells.

Background on CAR$^+$ T Cells for Cancer

CARs are genetically engineered T cell receptors designed to redirect T cells to target cells that express specific cell-surface antigens. In most approaches, CARs are transduced into donor lymphocytes and expanded *ex vivo* before being transfused back into the patient (Fig. 1). CAR$^+$ lymphocytes function by inducing MHC-independent cytotoxicity. First-generation CAR comprised an extracellular single-chain variable fragment (scFv) derived from an antibody that targets the surface of cancerous cells, linked to the intracellular domain of the T cell receptor (CD3ζ).[14–19] Newer CARs include intracellular costimulatory domains (e.g., CD28 and 4-1BB), which are important for lymphocyte activation and persistence.[15,16,18] Adoptive transfer of autologous lymphocytes genetically engineered with newer generation CAR has shown dramatic clinical benefit (67%, 6-month survival for relapsed/refractory leukemia compared with <25% with best

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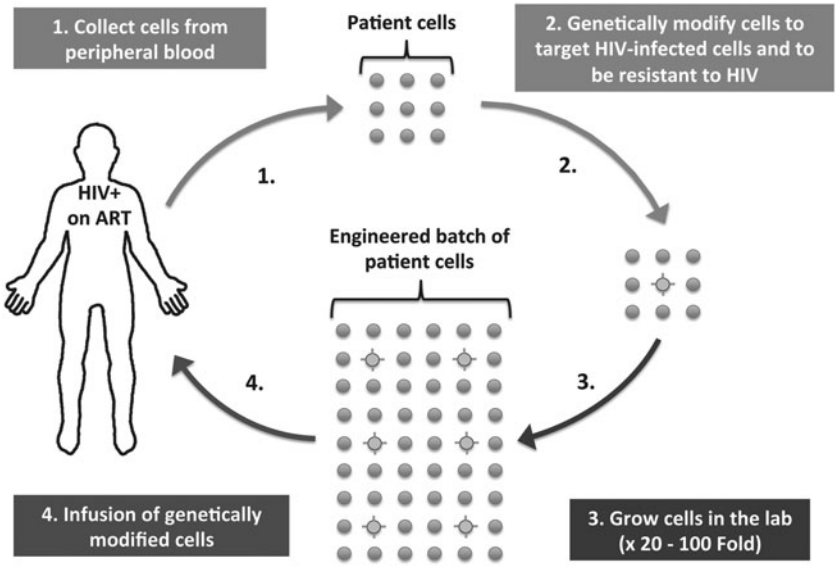

FIG. 1. Schematic representation of therapy for HIV with anti-HIV CAR-expressing cells. CAR, chimeric antigen receptor.

available chemotherapy[20]), and the efficacy of the CAR$^+$ T cells has persisted for >6 months in the majority of participants who did not undergo stem cell transplantation.[20–24] Analogous to cancer, adoptive transfer of lymphocytes engineered to express anti-HIV CAR may be able to persistently target HIV-infected cells that are expressing HIV or reactive and express HIV in the future.

Residual HIV Expression Despite ART is a Critical Barrier to Curing HIV

The majority of individuals on ART have no evidence of ongoing viral evolution,[25–27] which argues against persistent viral replication. However, most antiretrovirals function before viral integration and do not inhibit the expression of HIV proteins from infected cells. Residual viral expression likely explains the cell-associated viral RNA,[28–33] viral proteins,[34–38] and low-level plasma viremia (one to three copies of HIV RNA per milliliter of blood)[39–42] frequently seen during ART. Given the short half-life of free virions in the plasma,[43] the plasma HIV RNA concentrations during ART imply that tens of thousands of virions are produced per day, representing a major barrier to discontinuing ART without viral rebound. Although latently infected cells clearly exist[44] when ART is discontinued, high-level plasma HIV RNA normally returns within weeks,[45] mirroring the timeline observed with primary infection.[46] This suggests that cells actively producing virions exist and are likely an important target of efforts to cure HIV.

Mechanisms That May Allow Persistence of Residually Active HIV-Infected Cells

The paradigm has been that when long-lived latently infected cells reactive and express HIV, the HIV-infected cells are killed by cytotoxic T lymphocytes (CTLs) or direct virus-induced cell lysis.[47–49] On this premise, a variety of latency-reversing agents are being investigated as a means to eliminate latently infected cells.[50–55] However, Shan et al. demonstrated that HIV infection does not necessarily lead to cell death by either viral-induced cell lysis or autologous CTL-mediated effect.[56] Several biological mechanisms seem to limit the efficacy of CTL-mediated clearance of reactivated cells. First, HIV evolution selects for CTL-escape mutations,[57–60] which are less likely to be cleared by autologous CTL. Second, there is evidence that HIV Nef mediates downregulation of MHC-I,[61–63] which helps shield HIV-infected cells from CTL responses. Third, HIV-specific CTL responses may be ineffective, either because of exhaustion[64,65] or because of peripheral immune tolerance.[66,67] Therefore, new strategies that circumnavigate these limitations of the host immune response, perhaps in combination with latency-reversing agents, could be important in the effort to cure HIV.

Advantages of CAR$^+$ Lymphocytes to Target Residually Active HIV-Infected Cells

Anti-HIV CARs are appealing for three primary reasons. (1) CAR$^+$ CTLs function independent of MHC and can therefore target HIV-infected cells that are not effectively cleared by the host's endogenous CTLs (because HIV variants evolve to escape restriction by host CTL,[58–60] HIV Nef downregulates MHC-I expression,[61–63] immune exhaustion,[64,65] or immune tolerance[66,67]). (2) CAR$^+$ lymphocytes can retain cytotoxic activity for at least 6 months,[20,68,69] and CAR DNA has been detectable in the peripheral blood for up to 10 years,[70] potentially providing prolonged therapeutic benefit by targeting both the actively HIV-expressing cells and cells that reactivate in the future. (3) CAR$^+$ lymphocytes have also been found to traffic to the central nervous system,[23] a potentially important reservoir of HIV, that is difficult to treat with traditional pharmacologic agents.

Previous Trials of Anti-HIV CAR

The majority of CARs have been designed to target malignant cells, but since 1991, many anti-HIV CAR strategies have been described.[71–80] A Phase II randomized placebo-controlled clinical trial of a first-generation CAR to treat HIV-infected individuals on partially effective ART [only 62.5% (25/40) had viral load <50 c/mL throughout the study] demonstrated a significant decrease in infectious units per million peripheral blood mononuclear cells (–0.36 log; a commonly

used measure of the viable HIV reservoir) and rectal HIV DNA (–0.5 log), and a trend toward less viral rebound, although no decrease in peripheral blood HIV DNA or rectal HIV RNA.[81] Long-term follow-up suggests that this approach was safe and results in long-lived cells with CAR DNA that persisted for more than a decade.[70] However, no further clinical trials of anti-HIV CAR have been reported. More recent data have revealed that HIV can infect $CD8^+$ CAR T cells that express the CD4-zeta CAR used in the earlier trial,[82,83] which may have been an important limitation of this approach.

Previous Therapy with ΔCCR5 T Cells

Another cell-based approach to treating HIV is to adoptively transfer cells that are resistant to HIV infection. The most striking example of this was the use of naturally occurring homozygous ΔCCR5 cells for stem cell transplantation, which led to the only documented HIV cure.[84] However, a more practical methodology that is potentially scalable has been to collect patient cells, disrupt the CCR5 coreceptor *ex vivo* using a zinc finger nuclease, and then reinfuse the genetically modified cells. This approach appeared safe and feasible in a Phase I trial[85] and produced a population of HIV-resistant lymphocytes (13.9% of circulating CD4 T cells 1 week after infusion), which had an estimated mean half-life of 48 weeks. Whether there was an antiviral effect with this approach was not clear from the small Phase I trial. Efforts are under way to increase the number of HIV-resistant cells, or the half-life HIV-resistant cells, in order to determine if this approach can have a clinical benefit. It remains possible that producing a population of HIV-resistant cells will restore general CD4 function and achieve a ''functional cure,'' but that a ''sterilizing'' cure will require a population of cells that are both HIV specific and HIV resistant.

Combining Cell and Gene Therapy to Treat HIV

Anti-HIV CAR T cells that are also genetically protected from HIV infection is a strategy that several groups are now pursuing. Zhen et al. introduced a short hairpin RNA upstream of a CD4-zeta CAR, which targets CCR5.[83] Our group developed anti-HIV CAR T cells based on scFV from broadly neutralizing antibodies and engineered the cells to be ΔCCR5 (article in submission). In all cases, it is clear that the HIV-resistant CAR^+ T cells have better antiviral activity than CAR^+ T cells that are not engineered to be HIV resistant. These results demonstrate that CAR T cells can be infected by HIV and suggest that strategies which combine an HIV CAR with strategies to protect CAR^+ T cells from infection might be a promising path toward a cure. As shown in Fig. 1, these therapeutic approaches are complex, highly experimental, and there is real potential for toxicity; therefore, extensive *in vivo* testing in animal models and carefully controlled clinical trials is needed. There is excitement that clinical studies may begin within the next few years. Despite the tantalizing promise of cell and gene therapy to treat HIV, participants who volunteer for trials will have to be carefully counseled not to assume that these approaches will be effective and they will need to clearly understand the potential risks.

Author Disclosure Statement

No competing financial interests exist.

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