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The potential of radioimmunotherapy as a new hope for HIV patients

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Abstract

HIV/AIDS remains an enormous public health burden. Advances in anti-retroviral therapy (ART) have greatly reduced mortality and morbidity but HIV remains incurable, with patients suffering numerous disease- and treatment-related side effects. Any curative strategy for HIV must selectively eliminate existing infected cells. Radioimmunotherapy (RIT) is an established clinical modality in cancer treatment and has been shown to be effective in multiple infectious diseases models. We have recently demonstrated that RIT using a gp41-targeting antibody was effective and safe in eliminating HIV-infected cells *in vivo* (in mice), *in vitro*, and *ex vivo* in cells from HIV patients treated with ART. In addition, there is strong evidence that this radiolabeled antibody can eliminate HIV infected cells across the blood brain barrier. We consider RIT to be the most promising backbone strategy for HIV eradication.

Keywords

ART; eradication; HIV; radioimmunotherapy; reservoirs

Scope of the problem

HIV/AIDS remains an enormous public health burden. Advances in antiretroviral therapy (ART) have greatly reduced mortality and morbidity, but HIV remains incurable with patients suffering numerous disease- and treatment-related side effects. Nonadherence, emergence of drug-resistant HIV variants and the high cost and long-term toxicity of treatment remain major challenges. Even with strict ART adherence, HIV patients are at

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significantly increased risk for cancer, osteoporosis, cardiovascular disease and other end-organ diseases [1]. Because administration of ART prolongs the life of patients with HIV without providing a cure, the burden of disease is expected to grow.

Infection persists in cellular & anatomic reservoirs

ART acts by blocking HIV replication steps and thus prevents infection of new cells, but it does not kill existing infected cells. Long-lived cell populations such as resting memory CD4 T cells can act as reservoirs, harboring infectious HIV even in patients with undetectable peripheral virus levels. These reservoirs are formed within the first months following HIV infection and, upon interruption of ART, will re-establish productive infection [2]. In addition to cellular reservoirs, there are anatomic reservoirs created by cell-to-cell spread and the inability of drugs to reach therapeutic concentrations in various tissues. The central nervous system (CNS) is particularly vulnerable as HIV neuroinvasion can occur within 10 days of infection, but the blood–brain barrier restricts passage of many ART drugs [3]. The resulting sustained viral replication increases the likelihood of emergence of drug-resistant strains that can infect the rest of the body and is directly associated with neurodegeneration and the development of HIV-associated dementia. Neurocognitive disorders affect over 40% of HIV patients in the USA and the prevalence will increase due to the longer life spans of HIV-infected individuals [4]. While early and aggressive treatment with ART can substantially reduce the size of the total reservoir by decreasing the initial population of infected cells and virus occlusion in areas of low ART access, a stable population of latently infected CD4 T cells appears unaffected by early ART [5]. With the recent failure of attempts to cure HIV via bone marrow transplants [6], new treatments that eliminate both anatomical and cellular reservoirs of HIV and do not require lifelong adherence to ART are needed.

Issues with targeting of reservoirs

Any curative strategy for HIV must simultaneously inhibit the spread of HIV to new cells and selectively eliminate existing infected cells. Currently, the dominant experimental strategies to eradicate viral reservoirs are pharmacological reactivation of latent HIV using agents such as the histone deacetylase inhibitors, enhancement of host defense mechanisms via immunebased therapies, and transplantation of genetically modified CD4 T cells or autologous stem cells [7]. However, it is still unclear if such methods will target all populations of infected cells, whether autoimmunity will develop, whether new cells can become infected as a result of the reactivation and how many rounds of treatment would be necessary. Most importantly, like ART-driven approaches, neither activation of quiescent cells nor immune stimulation directly contains a method to kill infected cells. The renewed interest in immunotoxins, which link bacterial toxins to HIV envelope-targeted antibodies, may lead to a solution [8]. Recent promising work by Denton *et al.* [9] found significant depletion of the systemic viral reservoir in BLT mice from combined ART and immunotoxin treatment although the challenges of complex chemistry, CNS penetration, linker instability with potential toxin-mediated collateral damage and inherent immunogenicity remain to be resolved. Since targeting all infected cells in a patient will

likely involve multiple cycles of viral depletion, the chosen HIV eradication method must be safe for repeated administration.

Potential of radioimmunotherapy

Radioimmunotherapy (RIT) is an established clinical modality with decades of use as a cancer treatment and was recently demonstrated to be effective in multiple infectious diseases models [10–12]. RIT is the systemic administration of radioisotopes conjugated to monoclonal antibodies (mAb), delivering cytotoxic doses of radiation to cells expressing the target antigen. Advantages of RIT include its versatility, with multiple antibody and radioisotope combinations, and its independence both of the immune status of the patient and of typical drug resistance mechanisms. The antibodies used as the homing devices in RIT are non-neutralizing and thus do not put selective pressure on the virus. Within the armamentarium of radionuclides used in hematology, α -emitters such as Bismuth-213 (^{213}Bi , half-life 46 min) are preferred to β -emitters such as Yttrium-90 (half-life 64 h) for single cell diseases as their shorter tissue track and higher linear energy transfer allows for more potent and specific targeting. The short half-life of ^{213}Bi is an additional advantage as radioactivity completely decays by 4 h post-administration. ^{213}Bi -labeled mAbs and peptides have been used in clinical trials for several oncological indications such as myeloid leukemia, melanoma and inoperable gliomas and have demonstrated efficacy and a lack of major side effects [13]. While RIT can cause both transient and long-term myelodysplasia, neutropenia and thrombocytopenia, the overall safety record of RIT is strong and is particularly important in light of the continuing high mortality and low success rates of bone marrow transplants and gene therapy approaches for treating HIV [14]. Proof-of-principle experiments using RIT to eradicate HIV infection identified a human mAb known as 2556 as a lead candidate for the RIT component [10,15]. 2556 mAb recognizes a highly conserved linear epitope of gp41, the HIV-1 envelope glycoprotein, which binds the entry coreceptor and mediates fusion. 2556 binds strongly to primary virions of HIV-1 clades A–H and efficiently competes with endogenous HIV antibodies in patient sera. As gp41 is expressed both on the surface of HIV virions and on infected cells, but not on uninfected cells, it presents an attractive target for RIT.

Radioimmunotherapy efficacy against HIV

When conjugated to ^{213}Bi , 2556 safely eliminated HIV-infected human peripheral blood mononuclear cells (PBMCs) implanted in SCID mice, with no hematologic toxicity based on platelet count [15]. Current studies examining the efficacy of RIT in the presence of clinically relevant ART combinations found that RIT resulted in potent dose-dependent death of infected cells for all drug conditions, with increased killing efficacy from cotreatment compared with ART or RIT alone. The *in vitro* observations were confirmed using PBMCs directly isolated from 15 HIV-infected patients under treatment with ART. RIT-mediated cell death correlated with over 95% reduction of viral levels in 13 of the 15 patient samples, with complete elimination of detectable infectious virus (<40 RNA copies/ml) in 11 samples [16]. Additionally, 2556 bound the chronically infected ACH2, J89-green fluorescent protein and THP89-green fluorescent protein cell lines, both when the cells were stimulated to activate HIV production and in unstimulated latent states,

suggesting RIT's potential for targeting the latently infected reservoir. Preliminary results showed that ^{213}Bi -2556 is also able to cross an *in vitro* human blood–brain barrier model and kill infected PBMCs and monocytes on the brain side without overt damage to the barrier [17]. If supported by data from future clinical trials in HIV patients, RIT would constitute the only methodology currently available for targeting the HIV reservoir in the CNS.

Future steps

The *in vitro* and *in vivo* successes of RIT against HIV are highly encouraging, and efforts are underway to secure funding for Phase I clinical trials to be conducted in parallel in patients with and without ART treatment. The development of RIT of HIV for clinical use will hold specific challenges. As Berger and Pastan suggested in their discussion of an immunotoxin therapy against HIV [8], it is likely that complete eradication of HIV will require a three-step approach consisting of cycles of cell killing, suspension of ART treatment and use of an agent to activate HIV expression in latently infected cells. Additionally, because it is presently unknown whether any macaque models accurately recapitulate the mechanisms of HIV persistence in humans, these studies will be best performed in humans rather than primate models. As evidenced by the relapses of the bone marrow transplant HIV patients [6], more sensitive HIV detection methods will be necessary to identify all locations and forms of infected reservoirs in treated patients. While the latency activation/RIT/ART process will undoubtedly require optimization, diseases such as childhood leukemia have similarly complex multistep regimens which now save over 90% of patients from a previously incurable disease [18]. Given the enormous long-term cost and significant toxicity of life-long ART treatment and the dearth of cytotoxic agents against HIV, RIT holds significant potential to fill a very important gap in the fight toward a cure for HIV.

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Biographies

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