Cancer Research May Offer Clues to an HIV Cure—and Vice Versa

Cancer and HIV are invaders that the immune system fails to detect, and the similarities don't end there.

August 9, 2017 By Liz Highleyman

There is a growing overlap between the fields of cancer and HIV cure research, and approaches that help fight one disease may offer clues about the other. This convergence was the theme of the HIV Cure and Cancer Forum preceding the International AIDS Society Conference on HIV Science (IAS 2017) last month in Paris—the first time cancer has joined the HIV cure agenda.

"The molecular basis is completely different, but how we achieve a cure may be similar," said Monsef Benkirane, PhD, of the Institute of Human Genetics in Montpellier, France.

A common thread between cancer and HIV is that the immune system fails to get rid of something in the body that shouldn't be there. Viruses such as HIV are completely foreign, and while cancer arises from human cells, tumors develop mutations and express markers that distinguish them from normal cells. In both cases, the immune system is unable to recognize and respond to the invader.

Another commonality is that even if the immune system does a partial job, a single cancer cell or a single T cell harboring HIV DNA is enough to rekindle the disease. And determining where these residual cells may be hiding is a major challenge for both cancer and HIV researchers.

The cancer field is currently undergoing a paradigm shift, said Aurélien Marabelle, MD, of Gustave Roussy, the largest cancer center in France. Treatment has moved from traditional chemotherapy that indiscriminately kills fast-growing cells, to targeted therapies that work against tumors with specific genetic characteristics, to immune-based therapies that "help patients fight their own cancer," he said.

These new types of therapy may be better tolerated than traditional chemotherapy, which kills not only cancer cells but also rapidly dividing healthy cells throughout the body, including the gut, bone marrow and hair follicles.

But immune-based cancer therapies don't work for everyone, and it's not yet clear why this is the case or how to predict who will benefit. Another drawback is that drugs that stimulate an immune

response can act too broadly, leading to excessive inflammation of healthy tissue. While oncologists know how to manage toxic chemotherapies, they are still learning how to deal with immune-related side effects, Marabelle said.

Clinical trials of new immune-based therapies can be challenging because drugs that work well for a small subgroup of patients may not meet the threshold for overall effectiveness and therefore do not get approved and are not reimbursable by insurance. But people with cancer can learn from AIDS activists about how to gain access to new treatments more quickly.

“We need the same kind of patient advocacy to move regulatory agents faster than they are now,” Marabelle suggested.

On the HIV side, modern antiretroviral therapy (ART) is highly effective and well tolerated, but it can only control HIV replication, not eradicate the virus. HIV integrates its genetic material into the chromosomes of host cells and uses the cell’s machinery to produce new virus. Sometimes the virus integrates into long-lived memory T cells that enter a latent, or resting, state, creating a viral “reservoir.” If these cells later reactivate, the hidden HIV DNA can become active as well, producing new virus and rekindling infection.

Common Strategies
Several strategies are being explored to cure HIV, or more likely, to bring about long-term remission after stopping ART, known as a “functional cure.” These include activating resting T cells to flush out the hidden HIV and then helping the immune system find and destroy the virus—known as the “shock and kill” approach—or, alternatively, keeping the virus permanently locked away so it can’t reactivate.

A number of small-molecule cancer medications have been tried as a way to reverse T cell latency. These include drugs that affect epigenetics (how genes are expressed), such as histone deacetylase, or HDAC, inhibitors. But numerous studies have shown that although these agents can wake up latent T cells and make them produce new HIV, this does not seem to reduce the size of the viral reservoir.

Checkpoint inhibitors, at the forefront of cancer research, are also being studied as an HIV cure strategy. The PD-1 (programmed death) receptor is an immune checkpoint on T cells. Under normal circumstances its role is to stop excessive immune response against healthy tissues and dampen the response to infectious organisms after the immune system has done its job.

PD-1 is heavily expressed on “exhausted” T cells that have lost their ability to function. Some tumors can hijack PD-1 to turn off immune responses against them. Checkpoint inhibitor drugs like Keytruda (pembrolizumab) and Opdivo (nivolumab) that block PD-1 can release the brakes and restore T-cell activity against cancer cells.

Another approach involves JAK inhibitors such as Jakafi (ruxolitinib) and Olumiant (baricitinib), immunomodulating drugs used to treat myelofibrosis (a bone marrow cancer) and graft-versus-host disease after a stem cell transplant. Christina Gavegnano, PhD, of Emory University in

Atlanta, reported that baracitinib reduced the number of CD4 cells harboring latent virus in recently infected monkeys. The drug could potentially help shrink the HIV reservoir enough so that antiretrovirals could be discontinued.

Marabelle said that so far immune-based therapies have been used like chemotherapy, treating patients until disease progression occurs or treatment becomes too toxic. But sometimes the response to immune-based therapy continues after stopping treatment, and it may not be necessary to treat for so long. These drugs may "recalibrate" the immune response so it remains active against cancer even after treatment ends, he suggested. Shorter therapy might reduce side effects and address the "financial toxicity" of expensive drugs.

PD-1 is also involved in suppressing CD8 (killer) T cells that target HIV. Animal and human studies have shown that blocking the interaction between PD-1 and its ligands, or binding partners, can restore T-cell proliferation and activity against the virus, leading to a reduction in viral load. PD-1 is also heavily expressed on CD4 (helper) T cells that harbor hidden HIV, and it appears to play a role in maintaining latency.

Timothy Henrich, MD, of the University of California, San Francisco reported that in an HIV-positive lung cancer patient treated with Keytruda, PD-1 expression on CD4 and CD8 T cells decreased and HIV-specific T cell responses increased but there was no sustained reduction in the viral reservoir. Two other people treated with the same drug saw little change. A French team saw similar results in two out of 12 HIV-positive lung cancer patients treated with Opdivo.

CAR-T (which stands for chimeric antigen receptor T cells) is another approach being studied in both cancer and HIV cure research. In fact, this approach was initially developed by Carl June, MD, now at the University of Pennsylvania Perelman School of Medicine, as an attempt to cure HIV.

CAR-T uses gene therapy to modify a patient's T cells. A sample of these cells is removed from the body, altered in the laboratory and infused back into the patient. T cells can be modified to recognize antigens on cancer cells or engineered to make them resistant to HIV infection.

A Food and Drug Administration advisory committee recently recommended approval of the first CAR-T therapy for cancer. Known as CTL019, or tisagenlecleucel, this therapy led to remission in more than 80 percent of children with advanced B-cell leukemia in a Phase II study.

Bone Marrow Transplants

Bone marrow transplants are too dangerous for otherwise healthy people with HIV who are doing well on antiretroviral treatment, but they can offer clues in the search for an HIV cure. This kind of transplant led to the only known existing cure in a man named Timothy Ray Brown, also known as the Berlin Patient.

Transplants of bone marrow, which is rich in blood-forming stem cells, are used to treat advanced leukemia and lymphoma. Strong chemotherapy kills off a patient's cancerous T cells or B cells, and the donor stem cells essentially rebuild a new immune system. This treatment is risky because the

chemotherapy leaves the patient prone to infections and the donor's immune cells can attack the recipient, a condition known as graft-versus-host disease.

Brown was on effective antiretroviral treatment when he was diagnosed with leukemia in 2006. It occurred to his doctor to give Brown a bone marrow transplant from a donor with a natural genetic variation called CCR5-delta32. People with this mutation are missing the CCR5 co-receptor on their T cells, making them resistant to HIV infection.

Brown stopped ART when he got his first of two bone marrow transplants. Ten years later, despite extensive testing, researchers have not been able to find replication-capable HIV anywhere in his body. But it remains unclear whether its disappearance was due to the use of CCR5-delta32 stem cells, strong chemotherapy, a graft-versus-host reaction or a combination of factors.

Brown's case provided a proof of concept for an HIV cure, but attempts to replicate it have not yet been successful. Henrich previously reported on two Boston men who received normal (not CCR5-delta32) stem cell transplants to treat lymphoma. After extensive testing failed to find HIV anywhere in their bodies, they stopped ART under close monitoring. Following an initial delay, viral rebound eventually occurred after three and eight months, respectively. Another man who received a bone marrow transplant for leukemia was able to stay off antiretrovirals for about 10 months before his HIV returned.

At the Paris forum, Maria Saldago, PhD, of the IrsiCaixa AIDS Research Institute in Barcelona, reported on a group of 23 HIV-positive people who received bone marrow transplants for cancer. Of the six patients who remained alive and were followed for more than two years, five of them show no evidence of remaining HIV. But they have not yet tried going off antiretrovirals, which will be the true test of whether they are cured.

A final commonality between cancer and HIV cure research is that most experts think the best results will be achieved with combination therapy. For cancer, this may include combinations of traditional chemotherapy, targeted therapy, checkpoint inhibitors and anti-tumor vaccines. For HIV, it may include very early antiretroviral therapy, drugs that flush hidden HIV out of resting cells and immune-based therapy or vaccines to help T cells recognize and control—or ideally eliminate—the virus.

"There are a number of questions we have in common that don't have answers," said Françoise Barré-Sinoussi, MD, who was awarded a Nobel Prize for the discovery of HIV. "We can learn from research in oncology, and I think our colleagues in oncology can learn from us in HIV."

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