Medical News & Perspectives

Men With HIV Age Faster According to DNA Methylation Study

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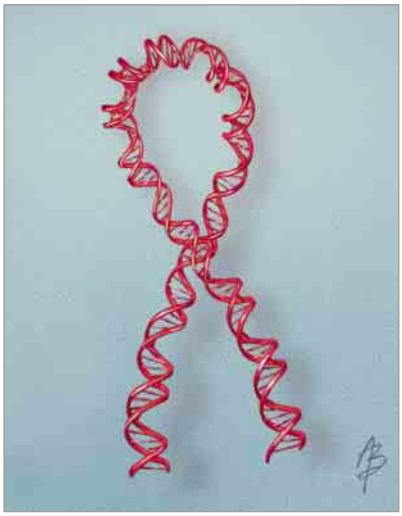
Infection with HIV may be associated with accelerated cellular aging, according to a new study in which researchers analyzed DNA methylation patterns of men with HIV infection (Gross AM et al. *Mol Cell*. 2016;62[2]:157-168). The study provides a possible explanation for why people with HIV who take antiretroviral medications often develop age-related conditions such as cardiovascular disease, hypertension, bone fractures, and renal failure years earlier than those who are uninfected (Guaraldi G et al. *Clin Infect Dis*. 2011;53[11]:1120-1126).

DNA methylation is an epigenetic change that governs gene expression over time (Jones MJ et al. *Aging Cell*. 2015; 14[6]:924-932). DNA methylation serves as a sort of "molecular wrinkle" that can be used to measure biological aging, explained Trey Ideker, PhD, chief of medical genetics and professor of medicine and bioengineering at the University of California, San Diego, and one of the study's principal investigators.

"It turns out as you age, these marks on DNA change quite a bit. You can use them as a kind of clock," said Ideker, who was involved in a 2013 study that found methylation patterns could be used to predict chronological age within 3.9 to 4.9 years with 91% to 96% accuracy (Hannum G et al. *Mol Cell*. 2013;49[2]:359-367). Furthermore, related research by a different research team found that individuals whose cellular or biological age, as measured by DNA methylation, was 5 years older than their chronological age had a 16% greater risk of mortality independent



of other risk factors such as education, diabetes, hypertension, and cardiovascular disease (Marioni RE et al. *Genome Biol*. 2015;16:25).

Epigenetic Clock Speeds Up

These studies set the stage for using methylation patterns to investigate whether people with HIV age faster biologically than those uninfected, said Ideker, who for the new study collaborated with Howard S. Fox, MD, PhD, a professor and executive vice chair of pharmacology and experimental neuroscience at the University of Nebraska Medical Center in Omaha.

Their research team took whole blood samples from 137 non-Hispanic white men aged 25 to 68 years who were infected with HIV and taking antiretroviral therapy. In addition, they took blood samples from 44 healthy non-Hispanic white men not infected with HIV. The research team then isolated DNA from these samples and analyzed genome-wide methylation patterns using molecular techniques.

The results demonstrated that the biological age of HIV-infected men taking antiretroviral therapy is, on average, about 5 years ahead of their chronological age, resulting in a 19% increased risk of mortality. In contrast, the biological and chronological ages of their healthy counterparts were closely matched. All but 15 of the HIV-infected men had some degree of advanced aging, Ideker said.

"The beauty of this [methylation] marker is that it is a very quantitative, quick assay," said Ideker.

The methylation data are what HIV researchers and clinicians needed to validate anecdotal observations that people with HIV age faster, noted Fox.

"The epigenetic clock of the methylome predicts increased mortality or morbidity if it is accelerated, and [our study] really did show that this clock was advanced [in patients with HIV]," Fox said.

In addition to the accelerated aging in individuals with HIV, Ideker and Fox's team also found that the average rate of age acceleration was the same regardless of how long the person had been infected with HIV, which was unexpected.

"I am not entirely sure how to interpret this result," Ideker said, noting that perhaps the rate of advanced aging is constant across time or, alternatively, the assay did not have the power to detect

subtle differences in age acceleration between those who were recently infected and those who had been infected for many years.

Virus or Drugs?

What's not yet clear is whether this accelerated aging is due to the effect of the virus itself or long-term antiretroviral therapy.

Chronic inflammation resulting from viral infection may be driving the earlier onset of age-related morbidities in HIV-positive patients, noted Larry Corey, MD, professor of medicine at the University of Washington and past president of the Fred Hutchinson Cancer Research Center in Seattle. Corey directed the AIDS Clinical Trial Group in 1987.

"We know clinically that HIV causes a continued inflammatory response," Corey said.

Although it is possible that antiretroviral drugs may play a role in the accelerated aging, Corey said it is unlikely because this accelerated aging seems to occur among HIV patients no matter which combination of antiretroviral drugs they are using. Instead, he suspects that the reactivation of latent HIV reservoirs may play a role.

In any case, it's a moot point because HIV is deadly if patients do not take the antiretroviral medication, Fox stressed.

Another unanswered question is at what rate accelerated aging occurs among HIV-infected women and people of different racial backgrounds, noted Carl Dieffenbach, PhD, director of the division of AIDS at the National Institute of Allergy and Infectious Diseases, who was not involved with the study.

"Women's aging is a little more complicated with the effect of estrogen," Dieffenbach said.

Interesting Directions

The study is sound and well done and points HIV research in "some interesting directions," commented Dieffenbach.

One finding with potential clinical implications Dieffenbach noted is that the human leukocyte antigen (HLA) genes, which regulate the acquired immune response, were hypomethylated in the HIV-infected men.

"The direction this points us in is what other diseases are associated with [HLA] hypomethylation?" Dieffenbach commented.

The researchers also discovered that hypomethylation is associated with HIV status and may be related to control of infection and subsequent inflammation. The inflammation caused by HIV infection in turn may be associated with the early onset of non–AIDS-related diseases such as cardiovascular and neurocognitive diseases in HIV-positive patients, Fox explained. He noted that this finding supports their overall conclusion that advanced biological aging predicts increased morbidity and mortality.

Another interesting question the study raises, Dieffenbach said, is whether the accelerated aging can be mitigated in people with HIV infection or if it is permanent.

"Did the virus take the human body down a pathway it can't recover from?" Dieffenbach said. "Even as the drugs have gotten better and better, HIV patients are left with this 5- to 7-year deficit in life span."

Slowing the Clock

Along these lines, findings from this study may encourage continued investigation of lifestyle and adjunct pharmacological interventions that could potentially delay the onset of age-related diseases in HIV-positive individuals, noted Ideker. For example, one study currently in progress is examining whether statins can reduce the risk of cardiovascular disease among HIV-positive adults aged 40 to 75 years who are taking antiretroviral therapy without a history of heart disease (http://www.reprievetrial.org). The National Institute on Aging has drawn attention to the possible link between inflammation and age-related diseases in people with HIV and is supporting studies of anti-inflammatory interventions such as aspirin and vitamin D (http://1.usa.gov/1SRXacL).

Ideker and Fox's study also suggests HLA genes might be a potential drug target for preventing the early onset of age-related diseases linked to chronic inflammation, Dieffenbach said.

"The hypomethylation of the HLA locus is telling us something about how HIV modifies the immune response, tipping the balance in favor of the virus," Dieffenbach said. "Targeting hypomethylation leading to better immunity for HIV disease as well as chronic diseases [such as heart disease] is a valid drug target."

Like a family history of a certain disease, the HIV-positive status of a patient should be viewed as an important risk factor for other morbidities, Fox commented, requiring clinicians to have "increased vigilance, increased prevention, and increased screening [for age-related morbidities]." ■

HIV and Transplantation: New Reasons for HOPE

Preeti Malani, MD, MSJ

Effective antiretroviral therapy has dramatically changed the health outcomes of people living with HIV. Although many HIV-positive patients now enjoy life expectancies similar to those of the general population, certain chronic diseases are more prevalent, and when present, these conditions appear to progress more rapidly. For example, co-infection with hepatitis C can result in liver failure, which is a major cause of death among people with HIV. Kidney disease is also common, with HIV-associated nephropathy being a leading cause of renal failure.

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For many with end-stage organ disease, transplant offers the best clinical outcome. However, years ago, organ transplantation was not felt to be medically feasible in patients with HIV because of concerns about disease progression with the need for added immunosuppression to prevent graft rejection. Slowly, this prevailing consensus changed, and organ transplantation from HIV-negative donors to HIV-positive recipients is now routine.

Nonetheless, people living with HIV who were suitable transplant candidates faced another hurdle: a severe shortage of donor organs. Like others on the waiting list, many died awaiting transplant. For HIV-positive patients in need of a transplant, there existed an untapped potential donor pool: other HIV-positive patients.