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Better than CRISPR? Another way to fix gene problems may be safer and more versatile

Epigenome editing flips genetic on-off switches in mouse studies

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Tools such as CRISPR that snip DNA to alter its sequence are moving tantalizingly close to the clinic as treatment for some genetic diseases. But away from the limelight, researchers are increasingly excited about an alternative that leaves a DNA sequence unchanged. These molecular tools target the epigenome, the chemical tags adorning DNA and its surrounding proteins that govern a gene's expression and how it ultimately behaves.

A flurry of studies in the past few years in mice suggests epigenome editing is a potentially safer, more flexible way to turn genes on or off than editing DNA. In one example described last month at a gene therapy meeting in Washington, D.C., an Italian team dialed down expression of a gene in mice to lower the animals' cholesterol levels for months. Other groups are exploring epigenome editing to treat everything from cancer to pain to Huntington disease, a fatal brain disorder.

Unlike DNA editing, where the changes are permanent and can include unintended results, epigenomic edits might be less likely to cause harmful offtarget effects and can be reversed. They can also be more subtle, slightly ramping up or down a gene's activity, rather than blasting it at full force or erasing it altogether. "What's exciting is that there are so many different things you can do with the technology," says longtime epigenome editing researcher Charles Gersbach at Duke University.

Adding or removing the chemical tags on DNA and the histone proteins it coils around (see illustration, p. 1035) can either muffle a gene, or expose its sequence of DNA bases to other proteins that turn it on. Some cancer drugs strip off or add these chemical tags, but as disease fighters they have had limited success. One problem is that the drugs are unfocused, acting on many genes at once, not just cancerrelated ones, which means they come with toxic side effects.

But epigenome editing can be made precise by harnessing the same enzymes that cells use to turn their genes on and off. Researchers attach key components of those proteins to a gene-editing protein, such as a "dead" version of CRISPR's Cas9 protein, capable of homing in on a specific place in the genome but unable to cut DNA. Their effects can vary: One editor might remove tags from histones to switch a gene on, whereas another might add methyl groups to DNA to repress it.

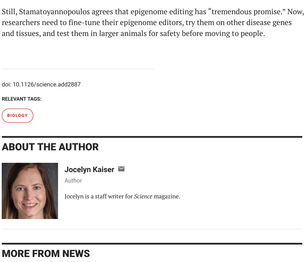
Two decades ago, the biotech company Sangamo Therapeutics designed an epigenome editor using this method that turned up a gene called *VEGF*, which helps promote blood vessel growth, in hopes of restoring blood flow in people with neuropathy from diabetes. The company injected DNA encoding the editor into the leg muscles of about 70 patients in a clinical trial, but the treatment didn't work very well. "We couldn't deliver it efficiently" to muscle tissue, says Fyodor Urnov, a former Sangamo scientist now at the Innovative Genomics Institute at the University of California (UC), Berkeley.

So the company turned to an adeno-associated virus (AAV), a harmless virus long used in gene therapy to efficiently deliver DNA to cells. The cell's proteinmaking machinery, the thinking went, would use DNA encoding an epigenome editor to make a steady supply of it. This strategy is looking more hopeful: In the past 3 years, Sangamo has reported that in mice, it can tamp down brain levels of tau, a protein involved in Alzheimer's disease, as well as levels of the protein that causes Huntington disease.

Other teams working with mice are using the AAV delivery approach to ramp up abnormally low levels of a protein to treat an inherited form of obesity, as well as Dravet syndrome, a severe form of epilepsy. Last year, a group used epigenome editing to turn off a gene involved in pain perception for months, a potential alternative to opioid drugs. Another team recently turned on a gene with an epigenome editor delivered by a different virus than AAV. They injected it into young rats exposed to alcohol; the alcohol was muffling the activity of a gene, which in turn left the animals anxious and prone to drink. The epigenome editor reawakened the gene and relieved the symptoms, the team reported in May in *Science Advances*.

Taking control

In epigenome editing, a gene-editing tool such as a "dead" version of CRISPR's Cas9 protein homes in on a gene. Next, an attached "effector" protein adds or removes chemical tags on DNA and histone proteins it coils around, turning gene activity up or down.



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The AAVs being tested by many groups are expensive, and these DNA carriers, along with the foreign proteins they encode, can trigger an immune response. Another drawback is that the loop of DNA encoding the epigenome editor is gradually lost in cells when they divide.

Last month at the annual meeting of the American Society of Gene and Cell Therapy in Washington, D.C., gene-editing experts offered an alternative to avoid the downsides of AAVs. A key step for the group, led by Angelo Lombardo at the San Raffaele Telethon Institute for Gene Therapy, came in 2016, when he, Luigi Naldini, and others reported in *Cell* that adding a cocktail of three different epigenome editors to cells in a petri dish repressed gene expression and that this endured as the cells divided.

This meant that instead of relying on AAVs to ferry in DNA for their epigenome editors—and force unending expression—they could use lipid nanoparticles, a kind of fat bubble, to carry its blueprint as messenger RNA (mRNA). In this way, cells make the protein for only a brief time, which is less likely to trigger an immune response or make epigenome edits in unintended places. Such nanoparticles are widely considered safe, especially after having been injected into hundreds of millions of people in the past 2 years to deliver mRNA for COVID-19 vaccines.

It took several more years for the Italian team to convert its lab study into success in an animal. At the genomics meeting, postdoc Martino Cappelluti from Lombardo's lab detailed how the team injected mice with fat particles carrying mRNA encoding epigenome editors designed to silence a live gene, *PCSK9*, that influences cholesterol levels. The strategy worked, with one injection suppressing blood levels of the PCSK9 protein by 50% and slashing low-density lipoprotein, or "bad," cholesterol for at least 180 days.

"I see it as a formidable advance," says Urnov, who hopes the lipid nanoparticle approach will soon be extended to other disease genes. "The key thing here is that you don't have to have continued expression of the epigenome editor," says Jonathan Weissman of the Whitehead Institute. Weissman co-led work reported last year in *Cell* on improved CRISPR-based epigenome editors that make long-lasting changes.

Researchers say epigenome editing could be especially useful for controlling more than one gene, which is harder to do safely with DNA editing. It could treat diseases like Dravet syndrome where a person makes some of a needed protein but not enough, because like a light dimmer, the strategy can modulate gene expression without turning it on or off entirely. Several new companies are hoping to commercialize treatments using epigenome editors. (Gersbach and Urnov founded one, Tune Therapeutics; Lombardo, Naldini, and Weissman are among the founders of another, Chroma Medicine.)

Despite the excitement, researchers caution that it will take time for epigenome editing to have a broad impact. The editors don't always work as advertised on some genes, says UC Davis epigenetics researcher David Segal. This may be partly because, as epigenetics researcher John Stamatoyannopoulos of the University of Washington, Seattle, worries, researchers don't understand exactly what the editors do once they infiltrate cells. "It's a black box," he says.

Still, Stamatoyannopoulos agrees that epigenome editing has "tremendous promise." Now, researchers need to fine-tune their epigenome editors, try them on other disease genes and tissues, and test them in larger animals for safety before moving to people.

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