Alert for athletes and astronauts: Gene editing moving into clinics, results promising

Gene editing has been in the news because of a new method that promises to develop into therapies for inherited diseases. Just like editing a written document involves changing and replacing letters, words, and sentences, gene editing means exactly what you would think it means. Many inherited medical conditions result from what are called “base pair substitutions”–replacement of certain genetic “letters” in a person’s genome with the wrong letters. This is different from knocking out a letter completely, or adding a letter, leading to what’s called a phase-shift mutation. By replacing the wrong, or mutated, genetic letters, with the correct letters, gene editing theoretically could cure a genetic disease.

Achieving this in all of a person’s affected cells is complicated. However, inspired by a system that protects the DNA of bacteria from viruses, the new method gets around the usual complications. It looks so promising that, in addition to beckoning as an upcoming cure for people afflicted with sickle cell anemia, cystic fibrosis, and other genetic diseases, it’s being considered for preventive treatment as well. This means treatment for those lacking symptoms, but at risk due to their genes. Or, the treatment could be useful for carriers, who usually don’t get sick, but might have symptoms in certain situations.

Novelty of the new method

Using agents, such as viruses, to carry a functional copy of the faulty gene into body cells, traditional gene editing methods often do not actually eliminate the faulty gene. The DNA with the new sequence either exists in the host cell distinctly from the chromosomes, or integrates into a chromosome. But, even if it integrates, it’s not always at the same location as the defective gene, nor does it replace the defective gene. Just as hand-editing a hard copy letter by writing the correct spellings alongside misspelled words does not leave a cleanly-edited document, traditional gene editing methods do not rid treated cells of the defective copy of the gene. This may not matter in cases when the defective gene, though unable to make a functional product, does not produce anything that’s detrimental. But if the defective copy of the gene is doing damage, simply adding a correct copy is not enough.

Used in research by a Cambridge, MA startup company called Editas Medicine and a team at Hiroshima University in Japan, the new technique is more like editing a document with a word processing program on a computer–just as I’m doing while writing this. It uses special protein molecules called programmable nucleases and specially sequenced RNA (a molecule similar to DNA) to achieve what’s called “gene knock in”.

Essentially, this means that any gene can be pasted into the genome of cultured cells, or cells of living organism, at the same time removing an unwanted sequence. Inspired by a similar system of molecules that certain bacteria use to protect themselves against viruses, the new system essentially does surgery on the faulty gene, cutting it out and replacing it. This capability is so powerful that it constitutes a sea change in the field of molecular medicine.

Technical and ethical challenges

On the technical side, challenges stem from the fact that the DNA cutting components in the new system (programmable nucleases) look for specific DNA sequences that surround the faulty gene sequence. Because similar sequences can be present in other parts of the genome, it's possible for the wrong gene to get replaced. Thinking of the programmable nucleases as molecule-sized surgeons operating inside the nucleus of cells, such a mistake would be the genetic equivalent of a surgeon operating on the wrong organ.

Based on results in cell culture, as well as in animals such as frogs and silk worms, the system is expected to become more accurate, and ultimately very safe. But, as with any treatment, the risk of ill-effects will never be zero. Thus, further down the road is a more complex issue of what to do for people who have some genetic risk, yet in whom a disease has not manifested. In cases of gene variants associated with certain diseases, often the disease never manifests at all. But what should be done for those with diseases for which the genetic variant is surely the cause of the pathology.

Take the sick cell gene as an example. This gene causes red blood cell precursors to make defective hemoglobin. What if you're a carrier, which is to say that you have the sickle cell trait – one copy of the gene for sickle cell hemoglobin and one normal copy of the gene. Under normal conditions, a person with sickle cell trait will never get sick. But, when stressed, due to extreme physical exercise, dehydration, or high altitude, people with sickle cell trait can have a sickle cell crisis. They can get sick, just like a person with sickle cell disease (a person who has two copies of the defective gene). For such a person, is gene editing warranted as a preventive measure? Maybe yes, maybe no, or it might depend on the person's lifestyle. An elite athlete, a mountain climber, an aspiring astronaut, or test pilot–any of these might be a good candidate for the preventive gene editing therapy.

Probably, these questions are merely the tip of the iceberg compared with the full collection of clinical trade-off issues and ethical dilemmas that will surface when efficient, reliable gene editing makes its way to the clinic. But it's a hint of things to come.

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