Scientists devise potential approach to treat spinal muscular atrophy

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In the neuromuscular disease called spinal muscular atrophy, or SMA, a protein deficiency caused by a single gene mutation leads to serious damage in growing nerve cells and the muscles they control.

Now, in laboratory experiments, researchers at Cold Spring Harbor Laboratory (CSHL) and Isis Pharmaceuticals have induced cells to replenish the protein by activating an existing, slightly modified copy of the mutant gene. These early results hold out hope for one day successfully treating this often-fatal disease.

SMA, which affects about one out of every 6,000 newborns, occurs when the baby inherits a defective version of a gene called SMN1 from both its mother and father. The protein that this gene produces performs cellular "housekeeping" activities, says CSHL professor Adrian Krainer, Ph.D., who led the research team, so "it's hard to explain why it matters more in motor neurons" that are afflicted by SMA than in other cells.

A Backup Copy

Some SMA patients are affected more profoundly than others, in part because a second version of the gene, SMN2, also produces the protein, and makes up for some of the deficit. "All these patients, although they're missing a critical gene, have this second gene that in healthy people is not necessary," says Dr. Krainer.

Over time, subtle mutations have arisen that make the second gene

produce much less of the critical protein, even though it still has all of the pieces needed to make the final protein. Instead, the mutations trigger the cellular machinery to omit one major piece of the protein, without which it rapidly degrades.

Researchers have known for years that some sections of the genetic information are left out during the intricate process that ends in the production of protein. The first step of this process, which is called transcription, involves copying DNA into a strand of RNA. This RNA is then “edited” by special enzymes that remove some sections and splice the others back together before the RNA is used to make protein. For many genes, the various sections can be mixed and matched, so that a single gene produces more than one kind of protein. Once considered a curiosity, this “alternative splicing,” of the RNA strand is now viewed as common, says Krainer, who is an expert on the topic.

Alternative Ways of Splicing RNA

When he first learned about SMA, Dr. Krainer says, "I was extremely excited, because I realized that what we knew about splicing could be applied" to the disease. All the researchers needed to do was to alter the splicing of the second copy of the gene to include the missing piece.

Dr. Krainer and his team sought to change the splicing by introducing synthetic molecules, called antisense oligonucleotides or ASOs, that precisely match various sections of the RNA. They reasoned that if these molecules stuck to the right part of the RNA, they might redirect the splicing process in the desired way. The researchers injected promising ASOs into mice that had an added, human version of the SMN2 gene. As they had hoped, the gene produced much more of the RNA for the critical protein, including the section that is usually omitted, in tissues where the ASOs accumulate.

Before this approach can be tried in patients, several additional issues must be addressed. Researchers will also need to find out, for example, whether the ASOs really benefit growing animals with SMA and how and when they should be administered to affect the nervous system. Still, in contrast to approaches that change splicing patterns for many genes, Krainer expects the highly targeted ASOs may have fewer side effects.

Source: Cold Spring Harbor Laboratory