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Researchers show efficacy of gene therapy in mouse models of Huntington's disease

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Researchers at the California Institute of Technology (Caltech) have shown that a highly specific intrabody (an antibody fragment that works against a target inside a cell) is capable of stalling the development of Huntington's disease in a variety of mouse models.

"Gene therapy in these models successfully attenuated the symptoms of Huntington's disease and increased life span," notes Paul Patterson, the Anne P. and Benjamin F. Biaggini Professor of Biological Sciences.

Patterson is the senior investigator on the study, which was published in the October 28 issue of the Journal of Neuroscience.

Huntington's disease is a neurodegenerative disorder with a genetic basis. The disorder has its roots in a mutation in a protein called huntingtin, or Htt. (The gene itself is also referred to as the huntingtin gene.)

All versions of the Htt gene have repeats of a particular trio of nucleotides—specifically, C, A, and G, which together code for the amino acid glutamine. In most people, that trio is repeated between 10 and 35 times. But in people who develop Huntington's disease, that genetic stutter goes on and on; they will have anywhere between 36 to upwards of 120 repeats.

The result of all these repeats? An abnormally long version of the Htt protein, which gets chopped up into smaller, toxic pieces and accumulates in nerve cells, debilitating them.

Enter Patterson group members Amber Southwell and Jan Ko, who began to look at the efficacy of two different intrabodies that had been shown, in cell cultures and fruit-fly models, to reduce the accumulation of toxic Htt protein. To see whether those effects would hold true in mammalian systems as well, the team tested the intrabodies in a series of five different mouse models of Huntington's.

One of the two intrabodies had some negative results, actually increasing Huntington's-related mortality in one model.

But the other intrabody—called Happ1—was an unqualified success, restoring motor and cognitive function to the mice, and reducing neuron loss as well as toxic protein accumulation. And in one model, it increased both body weight and life span.

Happ1 targets an amino-acid sequence unique to the Htt protein that is rich in the amino acid proline. Because of this, the action of Happ1 is expected to be extremely specific. "Our studies show that the use of intrabodies can block the parts of mutant huntingtin that cause its toxicity without affecting the wildtype, or normal, huntingtin—or any other proteins," says Patterson. In other words, he says, this has the potential to be the kind of "silver-bullet therapy" that many medical researchers look for.

This sort of research is of particular importance in the treatment of Huntington's disease, says Patterson. Despite the fact that this disorder has a single-gene origin, current treatments tend to address the symptoms of the disease, not its cause. That means it is currently impossible to prevent the disease from doing significant damage in the first place.

What's the next step in pursuit of this goal? "We need to improve the efficacy of the intrabody," Patterson says, "and we need to build a viral vector that can be controlled—induced and turned off—in case of

unexpected side effects. This is a general goal shared by all types of experimental gene therapies."

Source: California Institute of Technology (news : web)