HDBuzz

Huntington's disease research news. In plain language. Written by scientists. For the global HD community.

Lost in translation? New insights into the making of the Huntington's disease protein

Production of normal-length & extra-long huntingtin is controlled differently. A new way to keep cells healthy in HD?

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Everyone has two copies of the huntingtin gene but Huntington's disease is caused by a copy that's extra-long. New research shows that cells have different controls for how the normal and extra-long instructions are used to make protein. These controls on the protein-making process may be targets for developing drugs for HD.

You say potato…

We've known for twenty years now that the cause of Huntington's disease is a mutation in the **huntingtin** gene. In people who develop the disease, one of the two copies has a repeated section that makes the gene extra-long.

By analogy, if we were to write the normal huntingtin gene as the word 'potato', patients with HD would have one copy of huntingtin misspelled as 'potatato' or even 'potatatatato'.

The activity of helper complexes, which behave like assistant chefs when the cell is making a protein, is affected by the length of the huntingtin gene.

It's the extra-long copy of the huntingtin gene that makes neurons sick, because it causes them to produce an extra-long, harmful version of the huntingtin protein.

One problem facing scientists is to develop treatments that reduce the harm done by the extra-long protein, while preserving the useful functions of the normal-length protein. That's not easy to do, because the proteins are identical except for the repeated section. However, some new research by a German team, published in the journal Nature Communications, has shed some new light on this problem.

The making of a protein

To understand this new research, first we'll need to cover a few details about how cells actually make proteins.

The life of every protein starts off the same way, as a set of instructions written in the genetic code of the cell - our DNA. First, the cell makes a working copy of the DNA, made from a related chemical called RNA. This copying process is called **transcription**.

The RNA instructions float around the cell until they encounter a structure called a **ribosome**. When the instructions pair up with a ribosome, the ribosome uses them to assemble a protein. That process is called **translation**.

You can think of translation kind of like what happens when a chef prepares his world-famous chili: the chef (the ribosome) uses his favorite recipe (the RNA instructions) to make the chili (a protein).

Just like a chef sometimes has the help of an assistant chef when making his cuisine, ribosomes sometimes get a little bit of help making proteins. In these cases, the ribosomes join up with special **helper complexes** in the cell. The helper complex lets the ribosome translate genetic messages into protein more quickly than the ribosome could on its own.

A little help from my friends

With these details of translation in mind, a team of Huntington's disease researchers, led by Susann Schweiger of The Max Planck Institute for Molecular Genetics in Berlin, decided to study how huntingtin proteins are made from genes of different lengths.

As expected, they found that the normal and extra-long genetic instructions were both translated into huntingtin proteins when they met up with a ribosome (the chef from our analogy above).

During translation, however, the RNA instructions for **extra-long** huntingtin can also interact with a helper complex (the assistant chef from our analogy). This interaction wasn't seen with normal-length huntingtin RNA.

> “Because of the interaction with the helper complex, the cells made more extra-length than normal-length huntingtin protein.”

It turns out the the longer the RNA instructions are, the more they can interact with the helper complex. Because the helper complex makes translation more efficient, the result of this interaction was that the cells made more extra-length than normal-length huntingtin protein.

Lost in translation: reducing levels of extra-long huntingtin

The scientists wondered if they could affect levels of normal and extra-long huntingtin protein just by interfering with the helper complex.

Since the helper complex mostly interacts with the extra-length huntingtin instructions, interfering with it should reduce translation of the extra-long variety.

When the researchers blocked the helper complex using drugs, or prevented cells from making the helper complex in the first place, they got the result they expected - less of the extra-long huntingtin protein was made.

Decreasing extra-long huntingtin levels this way is appealing, because it happens before the protein ever gets made. If we could do it in people, it'd mean that extra-long or 'mutant' huntingtin would never even have a chance to make neurons sick.

Does this affect the search for HD treatments?

This research shows one effective way to alter production of normal and extra-long huntingtin selectively. It would be a form of 'huntingtin lowering' or 'gene silencing', but one that doesn't reply on DNA-like or RNA-like drugs, which are difficult to deliver to the brain.

In addition to the helper complex itself, scientists are also looking at targets that work further down the protein production line.

One such target is **mTOR** - a protein that is actually already on the scene as a potential target in Huntington's disease therapy.

One goal of 'huntingtin lowering' therapies research is to reduce production of the harmful version of the protein, while allowing cells to produce the helpful version.

We've known for a little while that drugs that interfere with mTOR decrease levels of mutant huntingtin protein by helping cells destroy it after it's made. The new research shows that these drugs may pack a second punch, too, by decreasing the amount of extra-long huntingtin that gets made in the first place.

mTOR is particularly tantalizing as a drug target because the FDA, which regulates which drugs can be used in humans, has already approved some mTOR inhibitors for cancer treatment and in organ transplants. If interfering with mTOR really is an effective treatment strategy, drugs that already exist could be repurposed for use in Huntington's disease.

Should we pop the champagne?

Not yet! First off, all of this new research on the role of the helper complex and mTOR in making extra-long huntingtin protein was done in cells or mice. These laboratory models are only the first step in understanding the human disease, so a lot of work remains before we'll know if these pathways are actually important for real people with Huntington's disease.

Second, even if these pathways are important, the other effects of drugs targeting these pathways may make it difficult to use them in Huntington's disease.

For example, the FDA-approved mTOR inhibitors described above work because interfering with mTOR is toxic and suppresses the immune system. That makes the drugs effective against cancers and for preventing transplant rejection. But since mTOR inhibitors would need to be taken for many years in Huntington's disease, these effects may make them unsuitable as HD therapies.

The bottom line

This work is a fascinating new approach that's moving Huntington's disease research in the right direction. The more we understand about how the normal and extra-long huntingtin proteins are made and work in brain cells, the better equipped we'll be in the search for HD treatments.

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

Glossary

huntingtin protein The protein produced by the HD gene.

gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

transcription the first step in making a protein from the recipe stored in a gene. Transcription means making a working copy of the gene from RNA, a chemical messenger similar to DNA.

ribosome A molecular machine that makes proteins using the genetic instructions in RNA message molecules

neuron Brain cells that store and transmit information

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
