mTORC1 tips the scales in Huntington's disease mice

Weighing the scales on mTORC1: A possible new target for HD therapeutics?

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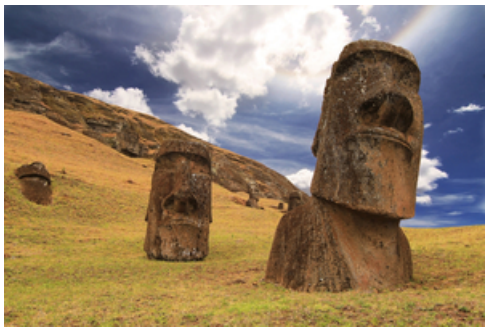
What happens when you have a broken part in a machine? You fix it! A new study shows that increasing the activity a critical piece of machinery called 'mTORC1' in a mouse model of Huntington's disease leads to improved motor problems and brain abnormalities associated with the disease. These recently published findings may offer scientists a new target for therapeutic development in HD.

In search of new targets

Everyone has two copies of a gene that scientists call "Huntingtin" and people with Huntington's Disease have inherited (at least) one mutant copy of this gene from either their mom or dad. The gene itself is not thought to be harmful, but rather what cells do with it. In general, cells use genes as instructions to guide the construction of little machines called proteins.

Like the gene, the protein made from it is called "Huntingtin", which can be a bit confusing. The mutant huntingtin protein builds up over time and especially damages a brain region called the striatum. Inside the cells of this important brain region, the mutant huntingtin protein can interfere with many other bits of important machinery that influence how a cell grows and survives.



mTORC1was initially discovered as the target of an antibiotic drug called "rapamycin". Rapamycin was originally isolated from a soil sample taken from Easter Island (or "Rapa Nui")!

Malfunctions in the work of these little machines caused by mutant huntingtin is thought to underlie the disease. Because of this, many researchers focus their studies on finding the broken cogwheels in cells with mutant Huntingtin around. What changes can be observed when mutant huntington is present? If we fix those changes, does it lead to improvements in HD symptoms?

One of these targets was recently investigated by a team of scientists led by Dr. Beverley Davidson at the University of Iowa. The group's research focused on a little machine called 'mammalian target of rapamycin complex 1' or mTORC1.

mTORC-What?

Now what exactly is this mTORC1? In order for cells to grow, divide, and survive, they must ensure that they carefully use their resources in the right way. If there's lots of food around, the

cells can happily spend energy. On the other hand, in times when resources are scarce, cells need to be much more conservative and save their energy.

This balance between using and conserving resources is where mTORC1 comes in. It sits in the middle of an elaborate set of machinery present in every cell, constantly ensuring that the amount of energy used is matched to the amount of energy coming in. In a way, the machinery controlled by mTORC1 is sort of like the cell's banker, making sure that the books are balanced.

> "When mTORC1 activity was restored in the HD mice, brain areas that had begun to shrink and degenerate recovered. The treatment also positively affected movement behaviors."

A broken machine

Previous work by other scientists had implicated changes in this energy balancing pathway in HD. To get more information about why this was happening, Davidson's team first looked at the brains of HD patients and mouse models of the disease. They found evidence that the activity of the network controlled by mTORC1 was strongly reduced in the vulnerable parts of the brain in HD.

Next, they used viruses to deliver a powerful "on" signal to the resource control network in the brains of HD mice, artificially boosting the activity of mTORC1. When they did this, they could measure changes that showed them that their push had worked - the system was working more like it did in the brains of normal, non-HD, mice.

When mTORC1 activity was restored in the HD mice, brain areas that had begun to shrink and degenerate recovered. The treatment also positively affected movement behaviors, such as the ability to run on a rotating bar (a task that HD mice do not do well on). Many other problems often seen in HD mice were improved, including increased cellular energy production.

Davidson's team also found that other pathways in the cell that have previously been shown to be defective in HD were improved by this treatment. One of these important pathways is called *autophagy* and is basically an organism's biological 'junk' cleanup process. This is especially important because this autophagy pathway can help cells clear out mutant huntingtin itself, which might explain where all these benefits were coming from.

The protein mTORC1 helps cells maintain a careful balance of energy production and energy consuymption. In HD brain cells, it seems that this careful balance is disrupted.

Interestingly, previous work had predicted just the opposite result - that increasing the activity of mTORC1 would lead to reductions in autophagy. Just why the opposite result was observed in HD brains is a bit of a mystery, one that will probably reveal new aspects of how cells work.

Excitingly, some of the benefits of increasing mTORC1 activity were seen even when mice were treated after they'd already gotten sick. These results are important because they show that brain cells are capable of responding to treatment even after disease onset.

Balancing act

While this work is very exciting science, it is important to note that the activities of these systems lie in a very delicate balance. An earlier study of mTORC1 in the muscles of HD mice revealed increased activation. You heard right – these are opposite findings.

If this is also the case in humans with HD, it could be very hard to find a way to change the activity levels of mTORC1 in different ways in different tissues. However, what is clear is that Dr. Davidson's results suggest that mTORC1 pathway in the brain is impaired in HD, and that improving how the pathway functions as a protective effect.

What all of this research suggests is that the interaction between mTORC1 and huntingtin lies in a delicate balance and that repairing or restoring this pathway must be done at just the right level to avoid further harm. It's a 'Goldilocks effect' where mTORC1 levels need to be just right - either too much or too little is harmful!

> "What all of this research suggests is that the interaction between mTORC1 and huntingtin may be in a delicate balance and that repairing or restoring this pathway must be done at just the right level to avoid further harm"

Tipping the scales

Much work still remains to translate these exciting scientific findings into a therapy. One major issue is just how complicated these systems and targets are for scientists to study. For example, other neurological disorders such as Fragile X syndrome and autism both feature overactive mTORC1 activity, while mTORC1 is reduced in ALS and HD.

This exciting new science also reminds us that it's when we get unexpected results that we often learn the most interesting things. Answering the new questions raised by this study might open new avenues for developing novel therapies for HD.

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.