Astrocytes: The new star in HD research?

A new article summarizes what the Huntington's disease field has found about a type of brain cell called an astrocyte. These star-shaped cells help keep brain cells healthy and could be leveraged for developing new HD therapeutics.

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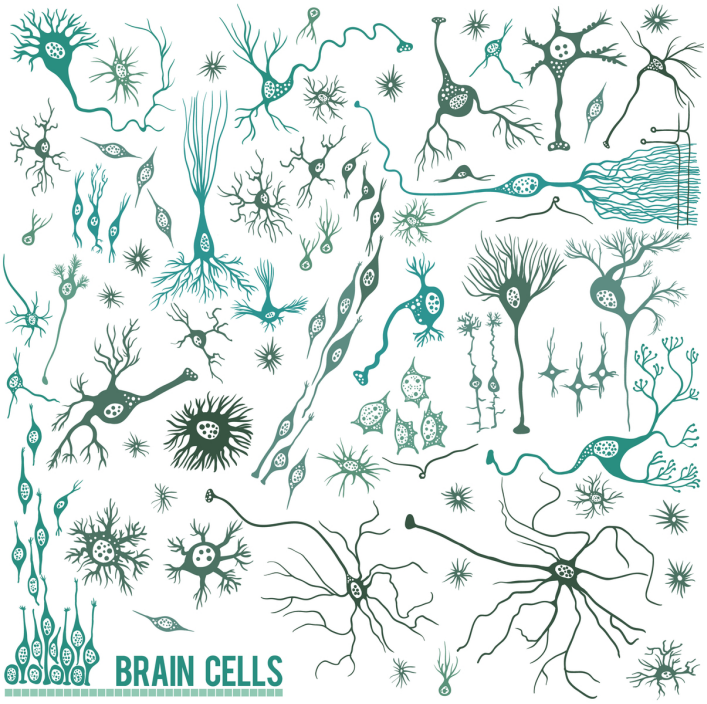
The most obvious changes related to Huntington's disease (HD) happen to neurons, the nervous system's messenger cells that send and receive information throughout the brain and spinal cord. However, many different cell types are affected by HD. A recently published article reviewed research findings from various labs, describing how a specific type of brain cell, called an astrocyte, contributes to HD. This review article details why researchers need to pay attention to more than just neurons to develop effective treatments for HD. Let's find out why!

The brain – more than just neurons

The huntingtin (HTT) gene is found in every cell in our bodies. That means that the expanded CAG repeat within the HTT gene that causes HD is also found in every cell. But there are certain organs, like the brain, that are more sensitive to being harmed by expanded HTT. Within the brain, there are certain regions that have proven to be particularly vulnerable in HD, such as the striatum – a portion of the brain that sits almost exactly in the center and helps control things like decision-making and voluntary movement.



While we typically think of neurons when we think about the effects of HD, there are many different cell types in the brain and each one expresses the HTT gene.

The striatum is made up of various cell types, including neurons, which we hear a lot about in HD. Neurons are the tree-shaped cells that transmit electrical signals allowing us to think, feel, and move. They also happen to be the cell type that's most affected in HD, losing their ability to function as the disease progresses. But the most abundant cell type in the striatum isn't neurons, it's actually a cell type called glia.

Glia are support cells that act to keep the brain healthy. There are several different types of glia, and newer evidence in the HD field has taught us that these different cell types also play a role in HD. Understanding how they contribute to HD and how they're affected throughout the disease could help develop new therapeutics.

Astrocytes are stealing the limelight

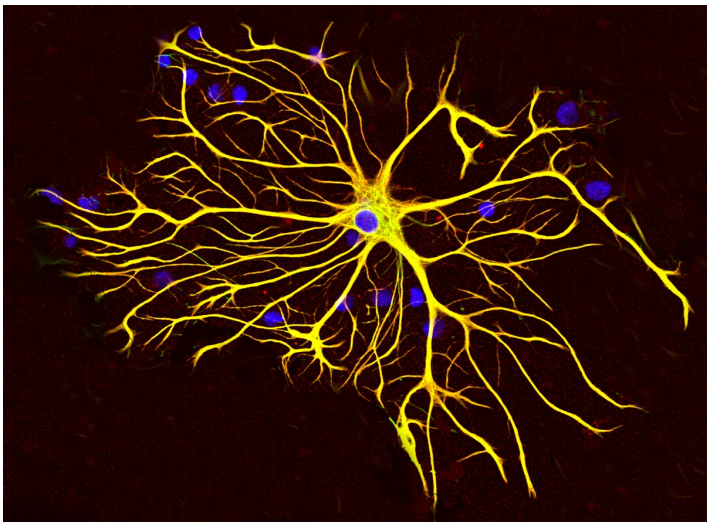
> **"An astrocytes motto is, "happy neuron, healthy brain"! "**

A particular type of glia that has gotten a lot of attention in HD research lately is a cell type called astrocytes. These are star-shaped cells that support neurons by making sure they have a nice environment in which they can thrive – they balance the chemicals around the neurons, provide nutrients, and protect them. An astrocytes motto is, "happy neuron, healthy brain"!

It takes a lot of astrocytes to make sure neurons in the brain remain happy and healthy. About 20-40% of the brain is made up of astrocytes! Unlike neurons, astrocytes continue to multiply throughout their lifetime. Also unlike neurons, astrocytes don't die in large numbers

over the course of HD, but they do appear to change. These changes are thought to alter their ability to support neurons and keep them healthy. Ultimately, those changes might contribute to the unique vulnerability of neurons in HD.

To summarize what the HD field has learned about astrocytes, Dr. Baljit Khakh from the University of California, Los Angeles and Dr. Steve Goldman from the University of Rochester teamed up to write a comprehensive review of scientific findings from the last 10 years on this topic. Drs. Khakh and Goldman are both experts in neurodegenerative diseases and have largely focused their careers on studying glia and astrocytes. Their review covered what we know about astrocytes from human brains and mouse models while suggesting how we can use this information to develop therapeutics.



Astrocytes support neuron health by regulating chemicals and nutrients within the brain.

Image credit: Gerry Shaw

Chicken or the egg

Tissue samples from people who have generously donated their brains to research have been instrumental in our understanding of astrocytes. These precious samples have taught us that in the HD brain, astrocytes change shape and lose the molecular "tags" that contribute to their unique identity. These changes in astrocytes progress with HD severity and are thought to reduce their ability to function properly. However, it's not clear from human brains if changes in astrocytes are a cause or consequence of the vulnerability of neurons in HD.

To understand cause and consequence between astrocytes and neurons in HD, scientists turn to animal models. Animal models allow researchers to ask and answer intricate biological questions that can't be done with human tissue samples.

Astrocytes – both cause and consequence

> **"The authors suggest that the most effective therapeutic strategies will likely require a two-pronged approach: lowering expanded HTT in neurons while**

> **restoring the ability of astrocytes to create a supportive environment in the brain. ”**

When they looked at astrocyte shape and function in HD mice, researchers found similar changes to what they saw in human brains. Researchers also discovered that changes in astrocyte shape were observed *before* neurons lose the ability to communicate. Additionally, researchers noted changes in potassium and calcium levels produced by astrocytes. Neurons use these elements to communicate throughout the brain and body. These findings may suggest that HD leads to changes in astrocytes that cause breakdown in neurons.

Using genetic manipulation techniques in mice, researchers lowered only the expanded copy of HTT exclusively in astrocytes or exclusively in neurons. This technique allowed them to tease out which cell type causes specific consequences of HD. Quite a clever tactic! They discovered that symptoms of HD in mice, like changes in behavior, primarily come from neurons and those changes in neurons disturb the function of astrocytes.

However these results seem to be a head scratcher - which comes first and which effects the other? It's a bit of a chicken and egg scenario. While it's not entirely clear if astrocytes or neurons are the cause or effect, it is clear that both cell types contribute to certain symptoms of HD *and* are affected by HD.

Researchers have found that animal models, like mice, do a good job of mimicking astrocyte problems in HD. The mouse astrocytes show similar changes in shape, function, and molecular tags that reduce their ability to create a supportive environment in the brain for neurons.

Another group used cell replacement to examine the role of astrocytes in HD. They transplanted non-HD astrocytes into a mouse with HD and found that the mice had fewer symptoms and lived longer. They also did the reverse experiment by transplanting HD astrocytes into a non-HD mouse and found that those mice developed HD symptoms. These findings suggest that at least some HD symptoms are caused by astrocytes and that replacing sick astrocytes could be an approach to consider to reduce HD symptoms.

Working together for effective treatments

The studies highlighted in this review paper suggest that animal models accurately mimic HD changes in astrocytes that we observe in humans. From these animals we've learned that neurons appear to be the primary drivers of HD symptoms. However, astrocytes themselves can also cause HD changes and their reduced function in HD further disrupts neurons.

The authors suggest that the most effective therapeutic strategies will likely require a two-pronged approach: lowering expanded HTT in neurons while restoring the ability of astrocytes to create a supportive environment in the brain. So while we might hear about certain therapeutic strategies more often, like HTT lowering, scientists all over the world are approaching therapeutics from different angles.

Work in the field is ongoing to fully understand the contribution that astrocytes have in HD. However, so far researchers have shown that both neurons and astrocytes are affected by HD. The cell types work together and understanding how each is influenced by the other can lead to the development of effective therapeutic strategies.

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

GLOSSARY

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

therapeutics treatments

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

neuron Brain cells that store and transmit information

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15