Enemy at the gates – huntingtin disrupts nuclear transport

Two recent studies show how a cellular border control system goes wrong in HD, opening new avenues for HD research.

By Tom Peskett | April 21, 2017 | Edited by Dr Jeff Carroll

Exciting new studies provide evidence that a particular kind of cellular trafficking goes awry in Huntington's Disease. Specifically, researchers have learned that traffic in and out of the cells control center - the **nucleus** - breaks down in HD. These findings open up new avenues for HD research.

Cellular border control

At the centre of every cell is a complex whirring hub of information storage and processing – the cell's nucleus. The nucleus is surrounded by a double-walled border, or membrane, which separates it from the rest of the cell. The nuclear membrane allows the nucleus to safeguard its precious contents, the molecule of life, DNA.

The nucleus is such an important part of the cell that it's kept behind a strong double-walled barrier with tight control over entry and exit.

The DNA is the instruction manual for making proteins that the cell needs to survive, grow and divide. Effectively, the nucleus needs to receive information on the status of the cell, decide which proteins need to be made and send chemical signals called **mRNA** (where the 'm' stands for messenger), back across the membrane where most of the protein production is carried out.

Overall, the nuclear membrane needs to allow useful chemicals through, while keeping potentially harmful chemicals, such as those that could damage DNA, out. To achieve this, cells have come up with a way to control the traffic crossing the membrane.

Each nucleus is studded with thousands of pores, which act as gateways in and out of the nucleus. In the same way a passport will allow a person to pass through a security gate at a border, proteins wanting to access the nucleus usually need to display a short sequence that will allow them to cross the pore. If they can present the correct sequence, a specialized protein escort will carry them across the pore. In the cell, this movement costs energy, like paying a toll. The downside of such a finely tuned border control system is that if it is compromised, it can spell disaster for the cell.

It is thought that as nuclear pores age, they lose their ability to selectively filter the traffic crossing them, which might contribute to normal human aging. People who inherit mutations disrupting the shape of the nuclear membrane age devastatingly fast, a condition known as **progeria**. Two recent studies from US-based teams put the focus squarely on HD, showing that the mutant huntingtin protein can cause major problems for the nuclear transport system.

Misshapen membranes

In the first study, led by Dr Jeffrey Rothstein from Johns Hopkins University, researchers looked at brain cells of aging mice, paying particular attention to the shapes of the nuclear membranes. They found that as the mice got older, the membranes became increasingly misshapen, seeming to develop buckles or creases.

> **“These results show that HD might speed up problems that are normally seen in aging cells ”**

They then repeated their experiment, but this time using HD mice, and found that abnormalities in the nuclear membrane were more common and appeared at an earlier age. Importantly, they saw the same effect when they compared cells from people with and without HD. These results show that HD might speed up problems that are normally seen in aging cells.

Shooting the messenger

To see if the changes in membrane shape affected transport across it, they looked atmRNA levels in the nucleus. As mentioned earlier, mRNA has to carry messages from the nucleus, across the membrane to the rest of the cell.

Normally the mRNA is found near the protein producing machinery in the cell, but in both human and mouse cells, mutant huntingtin caused mRNA to build up in the nucleus. This suggests that the transport of mRNA across the membrane might be blocked in HD.

How might this happen? The researchers looked at two proteins which normally help direct nuclear traffic, called Gle1 and RanGAP1. The first protein, Gle1, is an escort that helps mRNA get through the nuclear pores. The second, RanGAP1, ensures that there is a supply of energy available on the inside of the membrane, so that mRNAs traveling out of the nucleus can pay the 'toll' to get through the pores.

Both of these proteins seemed to stick to aggregates of mutant huntingtin found either in the nucleus or just outside the nucleus. This potentially stops them assisting mRNA through the pore, which might explain the nuclear mRNA build-up seen in HD cells.

In normally functioning cells, there is tight control over what goes in and out of the nucleus. To get past the guards, proteins must contain the right signals.

Interestingly, they found that the DNA, which is normally protected by the nuclear membrane, had accumulated more damage in HD cells. However, whether this was caused by the damaged nuclei or by other mechanisms (such as those described in this recent HDBuzz article: https://en.hdbuzz.net/233) is still unclear.

Leaky pores

In the second recent study, led by Dr Clotilde Lagier-Tourenne of Massachusetts General Hospital, researchers also looked at RanGAP1. They found, like the first study, that it stuck to mutant huntingtin aggregates.

They then focussed on the nuclear pores themselves – they saw that two proteins making up the pores also stuck to huntingtin aggregates and seemed to be scattered throughout the cell rather than localised to the membrane where the pores are. This suggests that the basic structure of the pores could be compromised in HD.

The researchers next went on to look at protein cargoes that get transported through the pore and found that the cargoes tended to be misplaced on one or the other side of the nuclear membrane, suggesting that the filtering mechanism of the pores might not be working effectively in HD, leading to 'leaky' pores.

Can nuclear transport be rescued in HD?

> **“It is always exciting to discover a completely new way in which HD causes cells problems, potentially opening doors to treatments. ”**

Finally, the researchers tested whether they could improve nuclear transport in their experiments. They found that by artificially increasing the levels of RanGAP1 - involved in the energy toll often required to cross the pore - they could reduce some of the negative effects of HD in flies.

Additionally, they were able to use drugs targeting nuclear transport to restore normal transport across the membrane in HD-like cells that had been grown in the lab. For example, a drug called KPT-350 prevents one of the protein escorts from carrying things out of the nucleus. The drug seemed to counteract the effect of the leaky pores, restoring the balance between the cargoes inside and outside the nucleus.

In Summary

It is encouraging that two teams arrived at the same important conclusion - that HD damages nuclear transport - from different starting points. Both studies used a variety of animal models and experiments, including cells derived from HD patients, so we can be fairly confident that HD has an impact on nuclear transport.

One team demonstrated, in principle, that nuclear transport defects could be targeted with drugs. However, these experiments were carried out on cells grown in the lab and further tests need to be carried out to see whether nuclear transport can be corrected in more realistic systems such as animal models.

It is still unclear exactly how the nuclear border control is compromised in HD. While these studies show that key parts of the transport machinery, such as RanGAP1 and Gle1, can stick to aggregates of mutant huntingtin inside the nucleus, another recent study suggests that only aggregates outside the nucleus harm nuclear transport. On the other hand, the two studies in this article were able to show that problems with nuclear transport can occur without any obvious aggregates. In future work it will be important to test the relationship between aggregates and nuclear transport.

It is always exciting to discover a completely new way in which HD causes cells problems, potentially opening doors to treatments. One certainty is that these new findings will create a flurry of research activity focused on nuclear transport defects in HD. We look forward to the next study.

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.

aggregate Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases

nucleus A part of the cell containing genes (DNA)

messenger RNA A message molecule, based on DNA, used by cells as the final set of instructions for making a protein.
