'Floating' gene-silencing drugs into the brain with exosomes

Exosomes – tiny bubbles made by cells – could be used to get gene silencing drugs from the bloodstream into the brain

By Professor Ed Wild | May 19, 2011 | Edited by Dr Jeff Carroll

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Many new drugs fail because they can't get into the brain – a major hurdle to developing new Huntington's disease treatments. Now, researchers have used exosomes – tiny bubbles produced naturally by some cells, to 'float'gene silencing drugs across the blood-brain barrier.

The blood-brain barrier

It's been said that the human brain is the most complex object in the universe. That complexity is what makes humans unique as a species, and each of us unique as individuals. But it comes at a cost: to keep working, the brain needs to maintain very strict control of its own environment - tiny changes in temperature, blood flow and the chemicals it lets in and out can cause big changes in the brain's functioning.

Exosomes are like tiny bubbles. Could they float through the blood-brain barrier to deliver drugs?

The **blood-brain barrier** is one way the brain keeps itself protected from the constantly changing outside world. The barrier is made from special reinforcements to the walls of blood vessels in the brain. Many chemicals can be absorbed from the stomach into the bloodstream, but hardly any can enter the brain from the blood - because of the blood-brain barrier.

The problem of delivery

While it might be good for us as a species, theblood-brain barrier is a nightmare for ‘drug hunters’. It means drugs that work well in the laboratory often don’t work at all when tested in humans - a familiar source of frustration for anyone who follows Huntington’s disease drug research.

There are several tricks already that can be tried, to get a drug to enter the brain, but none of them is perfect. One option is to alter the drug chemically so that it can cross the blood-brain barrier, but changing drugs in this way can reduce their ability to work once they’re in the brain. Another tactic is to inject the drug directly into the brain, or into the fluid that surrounds it - but that requires potentially dangerous brain surgery and the drug still might not spread throughout the whole brain. Viruses can be used to help drugs spread further, but can come with their own problems, like activating the immune system.

All in all, drug delivery and the blood-brain barrier are big problems for scientists working on any disease that affects the brain.

Exosomes

Step forward, **exosomes**. Exosomes are tiny particles, produced naturally by some cells. They’re used to transfer chemicals to other cells. To produce exosomes, the cell ‘squeezes’ a bit of its membrane then snips it off, a bit like a small bubble being generated from a larger bubble.

Cells can load the exosomes with cargo, and the exosomes can deliver that cargo into a cell it meets later. When we say exosomes are tiny, we really mean it - they are over a thousand times smaller than the width of a human hair.

So how might exosomes be able to help us to get drugs across theblood-brain barrier? These tiny bubbles can ‘float’ across the blood-brain barrier, so Dr Matthew Wood of Oxford University had the idea of using exosomes to deliver gene silencing drugs to the brain.

Gene silencing drugs

Our HDBuzz gene silencing primer will give you the full lowdown ongene silencing in Huntington’s disease. Put simply, gene silencing involves making drugs that consist of specially designed messenger molecules, that tell cells **not** to make a certain protein. In the case of HD, that would be the huntingtin protein. One approach to gene silencing is called **RNA interference** or **RNAi**.

Gene silencing has great potential for helping to protect brains against the effects of the Huntington’s disease mutation. But the blood-brain barrier is a big problem for RNAi drugs - if they are given by injection into the bloodstream, they don’t get into the brain. Even if they’re injected directly into the brain, they don’t spread very far.

Using exosomes to deliver RNAi drugs

> **“The exosomes zipped across the blood-brain barrier and switched off the right gene in the right place ”**

Like any package, a drug delivery needs three things: a container, a destination address and a cargo.

Wood’s team started with the container - the exosomes. They set up an exosome production line using cells purified from mouse bone marrow, called dendritic cells. Dendritic cells produce lots of exosomes naturally and are able to stay under the radar of the immune system, hopefully meaning that their exosomes will be similarly stealthy. The team grew the dendritic cells in the lab, then collected and purified the exosomes.

Next, the researchers needed to label the exosomes with a ‘destination address’ that would make sure they got to where they were needed. To target brain tissue, they genetically altered the dendritic cells so that they produced a protein from the virus that causes rabies. Because rabies is great at targeting the brain, the exosomes produced by these altered cells should be good at attaching to brain cells.

Finally, the researchers needed to load the exosomes with cargo. They did this by mixing the exosomes with an RNAi molecule and zapping the mixture with just the right amount of electricity. That made the exosomes absorb the drug molecules.

With the container, address and cargo in place, Wood’s team tested their RNAi-delivering exosomes on brain cells in the lab and found that they successfully delivered the drug to the right cells and switched off the right gene. But would they work in living animals?

In short - yes. When injected into the bloodstream of mice, theexosomes were found to be quite safe and, as hoped, didn’t cause a bad immune reaction. The targeting system worked well, too. Exosomes addressed to the brain zipped across the blood-brain barrier and switched off the right gene in the right place, and avoided other organs, even when their RNAi cargo could have switched off genes elsewhere too.

The real test came when the exosomes were used to deliver an RNAi drug aimed at switching off a disease-causing gene. It wasn’t the huntingtin gene they chose, but a gene involved in the development of Alzheimer’s disease, called BACE1. They chose BACE1 because reducing its activity is likely to protect against Alzheimer’s, but so far, all the drugs that act on BACE1 can’t cross the blood-brain barrier.

Again, the exosomes performed well. When injected into the bloodstream, they reached the brain, switched off the gene and even reduced levels of amyloid protein, which builds up in brains affected Alzheimer’s disease.

Summary

All in all, this research adds an important new piece to thegene silencing jigsaw. So far, exosome delivery hasn't been tested in a model of Huntington's disease, and it will need to be tested thoroughly to make sure it's safe, before it can be tried in humans.

But the idea of injecting a gene silencing drug into the bloodstream, and knowing that it will cross the blood-brain barrier and spread throughout the brain, is very appealing. HD researchers will doubtless be turning their attention to exosomes as one possible way of making gene silencing a reality for Huntington's disease patients.

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

GLOSSARY

blood-brain barrier A natural barrier, made from reinforcements to blood vessels, that prevents many chemicals from getting into the brain from the bloodstream

huntingtin protein The protein produced by the HD gene.

RNA interference A type of gene silencing treatment in which specially designed RNA molecules are used to switch off a gene

dendritic cell A type of cell that comes from bone marrow and is part of the immune system

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

bone marrow The gooey stuff in the middle of bones, that manufactures blood cells. When eaten, gives dogs a healthy coat and vitality

exosome Tiny bubble-like particles produced by cells that can transfer chemicals to other cells

amyloid The main protein that builds up in the brains of Alzheimer's disease patients

rabies A virus that infects the brain

BACE1 The gene for a protein called beta secretase 1, which thought to be involved in the development of Alzheimer's disease

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