HDAC inhibitors and a possible 'blood biomarker'

HDAC inhibitors explained, plus how new HDAC-related Huntington's disease research might help us find biomarkers

By Dr Ed Wild October 14, 2011 Edited by Dr Jeff Carroll

One way the Huntington’s disease gene causes damage is by interfering with the control of many other genes. HDAC inhibitors are drugs that aim to correct this, and researchers are working on bringing them to human trials. Meanwhile, the world of HDACs has produced an interesting lead in the search for biomarkers to help us test drugs.

The recipe book

A gene is a recipe, spelled out in DNA, that tells our cells how to make a particular protein. Proteins are the molecular machines that do most of the hard work inside cells.

Histones are like a lock that protects the ‘secret recipes’ in our DNA. Like a key, HDAC enzymes open the lock, exposing the DNA.

The HD gene is one of thousands that each of our cells carries. It’s a good example of how a small change in a gene can cause big changes in the body. In the case of HD, a small mistake in the gene - like a spelling mistake in a recipe - causes cells to produce the mutant huntingtin protein, which causes all the problems and symptoms of Huntington’s disease.

How genes are controlled

But there’s more to cooking than just following a single recipe. First, it’s important to choose which recipes in the book to follow, then you have to decide how much of each recipe to make. If you were holding a dinner party, it would be rather odd to cook twenty different soups and nothing else, or to prepare a meal for two people when you’re expecting a hundred guests.

It’s just as important that our cells choose the right gene recipes, and follow each recipe the correct number of times, to make sure that the right amount of each protein is made. It’s also important for cells to adapt because different situations call for different amounts of each protein.

The first step in reading a gene is to make a working copy from a DNA-like chemical called RNA. That’s called **transcription**. Controlling the activation levels of different genes is called **transcriptional regulation**. When it goes wrong, that’s called transcriptional **dys**regulation.

Transcription factors and histones

Cells have complex machinery for controlling gene activation levels that allow them to react to different situations. Proteins called **transcription factors** are important. When the time is right, they attach to specific places in our DNA, like you might put a bookmark in a recipe book. The cell then spots the bookmark and starts reading the gene. Other transcription factors tell cells not to read a particular gene, while some control many related genes all at once.

If you had a book of secret recipes, you’d want to keep it well protected, perhaps by padlocking it shut or locking it away. Cells are just as protective, and wrap their DNA round proteins called **histones**. Before a gene can be read, first the DNA has to be unwrapped from the histones.

Gene regulation problems in HD

Now imagine if you were cooking a meal from a recipe, but someone who was supposed to be helping you, kept you telling you to make twice as much as you need, or moving your bookmarks around so that you follow the wrong recipe. Chances are, that would end in a big mess.

In a way, that’s what happens in Huntington’s disease.

The mutant huntingtin protein behaves a lot like that unhelpful assistant. We know that one of the main ways in which mutant huntingtin causes damage is by messing up the activation levels of other genes.

> **“**A major effort is now underway to develop and test drugs that will inhibit HDAC enzymes safely ”

Partly, mutant huntingtin causes problems directly, by binding to the DNA like a transcription factor. And partly, it does it indirectly, by messing with other transcription factors.

The end result has been shown many times in Huntington’s disease - widespread chaos in the control of gene activation. And since each gene is important in its own way, you can see how these effects of the mutant protein could be very widespread and damaging to cells.

HDACs, exposing the DNA

As we’ve seen, histones are important in controlling what bits of our DNA are protected and what bits are exposed.

Histones themselves are controlled by a chemical switching process. A tag called ‘acetyl’ is attached to the histone or removed from it.

When a histone has an acetyl attached to it, it keeps the DNA protected. When the acetyl is removed, the DNA is more exposed.

The protein machines that remove the acetyl tags are called - brace yourself - **histone de-acetylase enzymes**. For obvious reasons they’re usually referred to as **HDACs** - pronounced “H-dacks”.

Because HDACs remove acetyl from histones, their overall effect is to leave stretches of DNA exposed and potentially vulnerable to the chaos caused by the mutant huntingtin protein.

HDAC inhibitors: protecting the DNA

Scientists working on treatments for Huntington’s disease have wondered whether it might be possible to prevent or reverse some of the gene activation chaos caused by the mutant huntingtin protein.

HDACs are particularly interesting, because a drug that reduced the activity of HDACs ought to protect the DNA against some of the chaos. Drugs that do this are called **HDAC inhibitors**.

Gene regulation problems contribute to the development of some cancers, and in fact two HDAC inhibitors are already approved for the treatment of certain blood cancers, with many more being studied.

> So far, HDAC-4 is the most promising drug target among the HDACs, when it comes to producing benefits with fewer side-effects.

HDAC inhibitors in HD mice

Many HD researchers see HDAC inhibitors as among the most likely to lead to successful treatments for patients.

Building on the work of others in yeast and fruit flies, in 2006 researchers led by Prof Gill Bates, of King's College London, published a landmark study of an HDAC inhibitor called **SAHA**. HD mice given SAHA in their food performed much better than usual on tests of movement.

However, the SAHA-treated mice lost more weight than expected - warning of toxic side effects if the drug were used in humans.

Harmful drug side effects might not be a deal-breaker in conditions like cancer, where treatment is usually in short bursts. But in HD they'd be a major concern, because ultimately we'd like to treat people with the expanded HD gene before they have any symptoms - and treatment may go on for years or decades.

Improving the drugs

There are many different histone proteins, and many different HDAC enzymes that behave differently and protect or expose different bits of DNA in different circumstances. SAHA is a general inhibitor across the range of HDAC enzymes.

But subsequent work by Bates' team, and others, has revealed one HDAC in particular - **HDAC-4** - to be particularly interesting. Disabling HDAC-4 genetically produced the benefits of SAHA treatment, without the weight loss.

A major effort is now underway to develop and test drugs that will inhibit HDAC-4 safely and without interfering with the other HDAC enzymes. It's hoped that this will lead to drugs to slow progression in HD while minimizing the risk of harmful effects.

So what's new in HDACs?

As well as requests for an HDAC article from HDBuzz readers, our attention was drawn to HDACs and HDAC inhibitors by a recent paper in the journal PNAS by Dr Clemens Scherzer of Harvard Medical School, Massachusetts.

Scherzer's group began looking for **biomarkers** of Huntington's disease. A biomarker is a test that can be used to measure or predict progression of a disease. We need good biomarkers so that we can test drugs more quickly.

> Drugs and biomarkers - tests that measure disease progression - are both difficult to find. Carefully designed studies can help us to find both.

Scherzer used some nifty technology called **expression profiling** to look at all the different RNA message molecules in the blood of HD patients. The amount of each RNA is a measure of how activated a particular gene is. One of the most common RNA types corresponded to a gene called **H2AFY**, which is the recipe for a histone protein called **macroH2A1**.

This was a big surprise, because if cells in HD patients are producing too many histones, it could really mess around with the control of gene activation.

Scherzer's team checked the result in several different ways, in blood and brain from humans and several mice, and every time they looked, they found evidence of more of the gene or more of the histone protein than expected.

When HD mice were given the HDAC-inhibiting drug **phenylbutyrate**, levels of the histone protein fell. And when measured in blood samples from a clinical trial of phenylbutyrate in HD patients that was performed several years ago, levels of the H2AFY message were lower when patients had been taking the drug.

So is H2AFY a biomarker?

Some news sources have reported that the H2AFY message molecule is a biomarker for HD - a blood test that will enable us to run clinical trials in HD.

Unfortunately it's not quite that simple - as Scherzer's team themselves point out in their paper. Finding biomarkers is almost as difficult as finding treatments, and each possible biomarker needs to be tested in many different ways. The most important test of a biomarker is whether it can predict whether a drug will work. Since no drug has worked yet, that's a bit of a catch-22. It means we have to design studies carefully, to develop and test our drugs and biomarkers at the same time.

For a test to be a useful biomarker, we need to understand exactly what it means. Right now, we have very little idea why there's more than expected of the H2AFY gene message, and the histone protein the gene is a recipe for. We have even less understanding of how these changes link up with what we know already about how HD causes damage.

Onward!

This is the kind of stuff that scientists love to get their teeth into. Gene activation chaos - a major way in which the Huntington's disease mutation causes damage. Histones shielding the DNA, HDAC enzymes exposing it and HDAC inhibitors hiding it again. The challenge of developing HDAC-4 inhibitors that are safe. And now a new mystery - the H2AFY gene message, linked to both histones and HDAC inhibitors, which might help us find useful biomarkers.

With many research teams around the world tackling the issue from different angles, you certainly haven't heard the last of HDAC inhibition.

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

Learn more

Article reporting success of SAHA treatment in HD mice by Prof Bates' group in PNAS (full article requires payment or subscription)
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- Glossary
- **transcriptional regulation** the mechanisms that control the activation levels of different genes
- **transcription factor** a gene-control protein. In response to signals from inside and outside cells, transcription factors attach to the DNA and cause specific genes to be more or less activated, producing more or less of the corresponding protein.
- **HDAC** histone de-acetylases (HDACs) are machines that remove acetyl tags from histones, causing them to release the DNA they're attached to
- **expression profiling** a technique that allows measurement of the activation levels of many thousands of genes at once
- **huntingtin protein** The protein produced by the HD gene.
- **phenylbutyrate** a 'non-selective' HDAC inhibitor that affects all HDACs without targeting any particular HDAC enzyme
- **clinical trial** Very carefully planned experiments designed to answer specific questions about how a drug affects human beings
- **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.
- **biomarker** a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.
- **histone** special proteins that our DNA wraps around to stabilize and protect it
- **acetyl** a chemical tag that can be added to proteins or removed from them
- **SAHA** an HDAC-inhibitor drug. Its full name is Suberoylanilide hydroxamic acid.
- **RNA** the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
- Read more definitions in the glossary

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