



Huntingtin grabs a hammer: DNA repair in HD

Huntingtin helps fix damaged DNA, a recent study suggests, under the direction of a gene repair protein called ATM.

By Dr Leora Fox | February 22, 2017 | Edited by Dr Jeff Carroll

DNA damage is a hot topic in HD – and new research offers an intriguing explanation. Canadian researchers have uncovered a potential role for huntingtin in the repair of DNA. They speculate that the normal protein is recruited to the nucleus to provide a supporting scaffold for a construction crew of DNA repair proteins. Mutant huntingtin can commute to the job, but can't perform.

Pinning down huntingtin protein

An irregular stretch of CAG repeats is the genetic source of Huntington's disease. The great mystery is how this simple addition to a single gene triggers the deterioration of specific brain regions that control mood, movement, and reasoning. HD research usually emphasizes the mutation, modeling the dysfunction that results in cells and mice. This approach continues to advance our understanding of HD, but equally important is the pursuit of huntingtin's normal function. What exactly is it supposed to be doing, and how is that activity disrupted in HD?

Huntingtin is a huge, multi-functional protein, and we know it's essential for the developing brain. Previous research has defined it as a mediator of transportation and communication within nerve cells. Importantly, huntingtin can also move in and out of the nucleus, the cell's control center, where DNA is stored. We don't know exactly why huntingtin needs nuclear access, but a recent study offers an explanation, pointing to a critical job: the repair of damaged DNA.



DNA can splinter or wear down, in minute but ceaseless increments, with dangerous consequences

Image credit: GEA construction

Overseeing DNA damage repair

DNA is continually in heavy use in order to construct cellular building blocks and modify molecular messaging. It frequently sustains damage that requires immediate mending – up to a million times per day – and there’s a whole crew of proteins involved in the upkeep.

In 2015, we reported on a gene that hangs out in the nucleus detecting DNA damage and recruiting repair proteins to fix it. This damage surveyor gene is called ataxia telangiectasia mutated, or ATM, and its levels were elevated in HD mice.

Though ATM directed other proteins to fix DNA damage, it also recruited proteins that would kill the cell if the damage was too great. In other words, in HD mice ATM acted like an overly zealous construction foreman, overstaffing the repair crew and calling in the demolition team. Consequently, halving the amount of ATM in HD mice improved their behavior and protected their brain cells.

While ATM was overseeing the chaotic renovation sites where DNA was damaged, mutant huntingtin was entering the nucleus. This led Canadian investigator Ray Truant at McMaster University to wonder whether ATM was calling huntingtin protein to the nucleus as part of the DNA repair crew. The lab’s previous work supported this idea: when DNA stress occurred in cells, huntingtin acquired a sort of temporary ID tag, called a post-translational modification, that would let it enter the nucleus. When they took a closer look, huntingtin and ATM appeared in the same spots within the nucleus. Could huntingtin be responding to the summons of ATM, and entering the nucleus to help repair DNA damage?

Huntingtin headlamps and the ATM foreman

Truant’s team, helmed by postdoctoral researcher Tam Maiuri, used an innovative method to pursue their hypothesis, using molecules called “chromobodies.” These can attach to specific protein targets and emit fluorescent light, illuminating working proteins that can be tracked under a microscope. In this case, it was like attaching a tiny headlamp to each

huntingtin protein inside the nucleus. One caveat is that this novel technique can sometimes be a bit toxic, but it's a completely new way to visualize huntingtin in living cells.

The researchers reasoned that if huntingtin itself is part of the DNA repair team, the glowing protein would travel to sites where DNA had been damaged, under the direction of ATM. To test this, they used an extremely precise laser light beam to irradiate each nucleus, etching a stripe of DNA damage in its wake. Soon after, they observed the arrival of glowing huntingtin proteins along the injured swath. ATM proteins were congregated in the same place. When a drug was used to silence ATM, huntingtin proteins didn't navigate to the DNA damage strip, suggesting that ATM might signal huntingtin to join the repair crew. ATM was not directly responsible for affixing huntingtin's ID tag to access the nucleus, so the enlistment of huntingtin probably occurs through an intermediary. The exact chain of command is the subject of future experiments.

Huntingtin's repair specialty

DNA damage comes in many varieties – imagine its double-helix like a wooden staircase beset by a gaggle of rough-housing kids. Something is bound to spill, splinter, or wear down, in minute but ceaseless increments, with potentially dangerous consequences. In the cell, negligent repair of DNA strand breaks, structural distortions, or incorrect additions could in extreme cases lead to cancer or even cell death. Huntingtin arrived along a lasered trench of severe, multifaceted DNA damage – but what type of repair was it there to support? Most proteins on the DNA repair crew have a specific forté, and Truant's team wanted to determine huntingtin's specialty.

“DNA damage was more persistent in HD cells than in normal ones, suggesting that mutant huntingtin is less efficient in its repair role ”

Other recent findings from the Truant lab suggested that huntingtin might enter the nucleus in response to stressors that can cause single-base DNA lesions. These lesions affect only one “letter” of a single pair in the genetic code, which might sound minimal, but now imagine a sharp nail protruding from one step on the wooden staircase. Single-base damage is repaired at specific locations by a process called base excision repair, or BER. To show that huntingtin could play a role in BER, researchers exposed cells to a chemical that causes single-base damage. Not only did huntingtin travel to sites where BER occurred, but it assembled alongside a crew of known DNA repair proteins. Only proteins on the BER renovation team became biochemically fastened to huntingtin. This suggests that huntingtin may act like a scaffold, providing a framework for other BER proteins to reach DNA sites that need work. Once again, huntingtin only arrived at repair sites when ATM was active, implying that it was recruited by ATM.

Mutant huntingtin comes to work and botches the job

In HD mice, lowering ATM levels was beneficial, perhaps because it dulled ATM's misdirected DNA repairs and zealous demolitions. But if huntingtin itself helps fix DNA lesions, perhaps there's a difference in how normal versus mutant huntingtin moves to the nucleus, or participates in the repair job. Maiuri reasoned that mutant huntingtin could be less mobile, or less efficient. To test this, she worked with normal and mutant skin cells donated by HD patients and their spouses.

It turns out that mobility was not the issue – mutant huntingtin navigated to sites of DNA damage just like normal huntingtin. However, the DNA damage was more dire and more persistent in HD cells than in normal ones, suggesting that mutant huntingtin is less efficient in its repair role than normal huntingtin. We're not exactly sure how, but it's possible that mutant huntingtin makes for a shaky scaffold, which could prevent the efficient mending of mangled DNA. Additionally, bulky mutant huntingtin might somehow get in the way of other important business in the nucleus. As with a prolonged delay in construction, now you've got a defunct structure and extra traffic. Whether mutant huntingtin is bad at its DNA repair job, or is causing drama around the worksite, it becomes a lose-lose situation for ATM to summon it to the nucleus. This could explain why lowering ATM levels in HD mice was beneficial.

Moving forward: studying DNA damage in HD

Overall, the data points to a potential role for normal huntingtin in DNA repair, and the authors were able to speculate on how the HD mutation might interfere with that function. More experiments will be needed to strengthen the link between ATM and huntingtin, and to understand how they might communicate about DNA repair in times of stress. While the chromobody technique is a novel and useful way to observe the movement of huntingtin, the overlap of two glowing proteins doesn't fully inform us about how and why they would interact. Huntingtin has many functions, and there's a chance that its presence in the nucleus alongside ATM and DNA repair genes is coincidental, or influenced by the chromobody technique.

Nevertheless, a direct link between huntingtin and DNA damage proteins like ATM is intriguing. The better we understand how normal huntingtin operates and with what cellular partners, the sooner we can design drugs that block or redirect the mutant form. Moreover, these findings are especially timely: mounting evidence from the field of human genetics suggests that DNA damage could play a role in earlier onset of HD. In short, DNA repair is a hot topic in HD with exciting therapeutic potential, and more detailed mechanistic experiments are sure to be forthcoming.

Drs Tamara Maiuri and Ray Truant are involved in HDBuzz. Dr Maiuri serves as an editor, while Dr Truant serves as External Scientific Advisor. Neither was involved in the decision

to write this story, its drafting or editing. [For more information about our disclosure policy see our FAQ...](#)

GLOSSARY

post-translational modification the addition of small chemical tags to a protein after it has been synthesized. These tags often change the location or function of the tagged protein.

huntingtin protein The protein produced by the HD gene.

nucleus A part of the cell containing genes (DNA)

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