Taking new targets to the bank: the DNA repair protein ‘ATM’ is overactive in Huntington's disease

HD causes the normally helpful protein "ATM" to get a little overzealous. Now we can look for drugs to settle it down

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A recent study by the Yang lab at UCLA points to a new idea for preventing damage to neurons in Huntington’s disease. The strategy is to tone down an overly helpful protein called ATM. Inside neurons, ATM provides a crucial role in repairing the cell’s infrastructure, somewhat like that of a bridge inspector, but the expanded HD protein may be causing ATM to misjudge DNA damage.

Nature’s inspectors, repair team, and demolition crew

ATM actually has nothing to do with a bank machine. ATM is an abbreviation for ‘Ataxia Telangiectasia Mutated’ because it is a gene that can cause a movement disorder called Ataxia Telangiectasia, but it may also play a role in Huntington’s disease.

Much like bridge inspectors, the job of the ATM protein is to detect structural cracks and breaks in DNA, and decide whether it should be repaired or condemned.

The function of ATM in the cell is something like a building inspector. When bridges get old they often rust, and parts need to be replaced to keep roads safe. Most bridges are inspected at least once a year by intrepid engineers with climbing equipment who determine whether or not a bridge can be repaired, or will need to be condemned.

Inside our cells, DNA shows wear and tear with age too, developing cracks and even breaks in the structure. This DNA damage occurs as part of the normal aging process, but it is seen earlier than expected, or more often than expected, in Huntington’s disease patients. DNA damage is also seen in HD cell and animal models.

The job of the ATM protein is to detect this sort of DNA damage, and then hang around the damage site, calling in a team of specialized proteins to do the repairs. If the damage is too great, ATM activates a different set of proteins, a sort of demolition crew, which condemns and removes the cells harboring the damaged DNA. It is a tricky business—an overzealous inspector could actually condemn a structure prematurely, while an unobservant inspector might fail to detect and repair structural damage.

Making the right call

Actual bridge inspectors usually communicate with their teams via walkie-talkie. In cells, communication is done by fastening chemical tags known as phosphate groups to the right proteins. ATM calls in the repair team by 'phosphorylating' a protein called H2AX. H2AX then settles down at the site of the structural DNA break and gets the repair started. If the damage is too far-gone, ATM can phosphorylate a different protein, called p53, which brings in the demolition crew instead of the repair team. The demolition crew shuts down the entire cell in a process called apoptosis, or programmed cell death. Needless to say, a lot of problems can arise if the demolition crew is called in by mistake.

The work done in the Yang lab shows that ATM signaling is increased in Huntington's disease, and this signaling may be going awry. When cells with the HD mutation were stressed, they showed more H2AX phosphorylation, and more cell death than expected. Excess H2AX phosphorylation was also found in brain tissue from HD patients, especially the portions of the brain that are known to be vulnerable in HD.

> **"**At this point, we don't know how the HD protein causes abnormal ATM signaling. But reducing ATM may be a promising new way to treat HD, and perhaps to prevent damage caused by the HD mutation. "

The question is whether extra ATM signaling in HD is a good thing, or a bad thing: in vulnerable brain regions, HD might cause more DNA damage, so ATM might be doing the right thing by signaling H2AX to make repairs. On the other hand, if overzealous ATM signaling is one of the detrimental effects caused by the expanded HD protein, then it could make a good target for a potential therapy.

Less is more

ATM is essential to normal health—patients with mutations in both copies of their ATM gene have a serious disorder called Ataxia Telangiectasia. Yet having only one functional copy of the ATM gene, a half dosage, doesn't seem to cause any symptoms at all.

With this in mind, the Yang lab set out to study ATM signaling in several ways. They started by reducing the amount of ATM produced in HD cells grown in a dish, and found that blocking ATM signaling actually made the cells healthier. Somehow, ATM signaling may have been calling in the demolition team rather than the repair crew in the HD cells.

The research team then looked at fruit flies with the HD mutation, which have trouble with their coordination when climbing up test tubes. They generated HD flies with a half dose of ATM (only one copy of the fly ATM gene). These flies were much better climbers than the regular HD flies.

> While bridge inspectors usually communicate with their teams via walkie-talkie, cells coordinate signals by fastening chemical tags known as phosphate groups to the right proteins.

Finally, when the researchers bred 'half dosage ATM' mice with HD mice, they found the most convincing results of all—the HD mice appeared healthy! HD mice with reduced ATM moved better, showed fewer signs of depression, had fewer aggregates, and less brain atrophy than the HD mice with normal amounts of ATM. In other words, having half of the normal ATM prevented some of the problems caused by HD.

Taking the ATM target to the bank

It is possible to reduce the activity of ATM with a small molecule drug, called an inhibitor. The researchers put ATM inhibitors on neurons grown in a dish and they found that it protected the cells from damage done by the HD protein. This opens the possibility for the development of an ATM inhibitor medication to treat HD.

At this point, we don't know *how* the HD protein causes abnormal ATM signaling. But two other studies have noticed the same thing, and this type of independent replication goes a long way to boost our confidence that we're on the right track. Together, the results of these studies suggest that reducing ATM may be a promising new way to treat HD, and perhaps to prevent damage caused by the HD mutation.

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