NEUROLOGICAL HEALTH

Could Trashing Junk Proteins Quash Alzheimer's, Parkinson's, ALS and Huntington's?

Scientists search for the Marie Kondo of the brain—a drug to clear cellular debris

By Esther Landhuis on July 26, 2016

Credit: MaryLB/Getty Images

Although clutter can be a nuisance, it does not typically pose a health threat—unless you're an aging neuron. As brain cells get older, some proteins within and around the cell misfold. They twist into the wrong shape, unable to do their routine job. Then they glom together to form menacing clumps. If left to accumulate, this "junk" can overwhelm nerve cells' quality control systems, triggering incurable brain disorders such as Alzheimer's, Parkinson's and Huntington's.

So whereas these diseases produce distinct symptoms and billions of dollars have been spent researching potential drugs that target their unique molecular culprits, some

scientists are placing their bets on cross-cutting approaches that might work across multiple disorders. Rather than going after proteins such as amyloid beta for Alzheimer's or alpha-synuclein for Parkinson's, one researcher has set on a different approach: "I settled on the idea that perhaps we should just get rid of as many abnormally folded, nasty-looking proteins as possible," says Karen Duff, a neuroscientist at Columbia University. Strategies that boost the cell's quality control programs, rather than disarm specific pathologic proteins, have looked promising in lab animals that serve as models for human neurodegenerative disorders including Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. Several molecules have entered human testing. It is still a long road to approved therapies but a growing body of basic research is fueling a search for drugs that interact with cellular cleanup processes to provide one-size-fits-all approaches for treating a megaclass of brain disorders.

Cells have two main systems for clearing excess or damaged proteins. Most of the quick cleanup occurs in cylindrical waste-disposal units called proteasomes, which chop unneeded material into smaller bits that can be recycled into new proteins. Proteasomes also keep cellular trash under control by breaking up misfolded proteins. When these scoundrels band together and the gang gets too large, the cell calls on a second degradation process—autophagy. Derived from Greek terms meaning "self-eating," the autophagy system sends protein aggregates and malfunctioning cellular components into acidic compartments called lysosomes, where enzymes chew them up.

In the early stages of Alzheimer's and other so-called proteinopathies—disorders caused by a malformed protein particular proteins adopt the wrong shape and join with similar misfits to form conglomerates that pile up in the brain. For awhile the cell's cleanup crews keep the junk at bay, sending protein aggregates for degradation as soon as they start to pile up. Rates of autophagy, however, slow with age. Over time, growing heaps of rogue proteins overwhelm the system and the cell gets sick and dies—or, at least, that has been the conventional thinking.

But the problem goes much deeper; it is not simply that freak proteins aggregate and clog the brain. Scientists are discovering that many of the proteins that twist out of shape normally carry out important jobs in the very disposal systems that are

supposed to help cells get rid of them, says neurobiologist Ralph Nixon of New York University. The problem has been traced down to the level of specific genes. Some disease mutations turn regular proteins awry by making them fold into the wrong shape. Misfolded proteins often misbehave, which can muck up the cell's cleaning system and make the organism more susceptible to any number of proteinopathies.

One famous misfit is presenilin-1. This protein is part of the enzymatic engine that churns out amyloid beta—a key molecular culprit in Alzheimer's disease—by snipping it out of a larger precursor protein called APP. Glitches in the presenilin-1 gene can cause the rare inherited form of Alzheimer's that strikes at a younger age. Apart from amyloid, though, presenilin-1 has a critical, beneficial function. Working with Ana Maria Cuervo, a professor at Albert Einstein College of Medicine, Nixon and co-workers found that presenilin-1 helps control the acidity of lysosomes. Neurons with abnormal presenilin-1 clear waste poorly and accumulate harmful protein aggregates. More recently Nixon's team discovered that APP hampers waste disposal systems in nerve clusters that falter and trigger memory decline in the early stages of Alzheimer's. Along with the earlier study on presenilin-1, these findings highlight the potential for therapies that target protein degradation pathways to help cells deal with buildup of harmful pathologic molecules.

The need for new approaches comes into stark relief as the Alzheimer's Association begins its annual conference this week in Toronto. Alzheimer's is a disease for which there are still no treatments that fundamentally alter the course of the disease, as trial after trial of drug candidates have ended in failure.

Research in Parkinson's and Huntington's has uncovered additional examples of disease proteins that, when mutated, stymie protein clearance pathways in neurons. Cuervo's group found that a mutant protein associated with a heritable version of Parkinson's gums up lysosomal channels. That leads the protein alpha-synuclein to build up and form toxic clumps in brain areas that control motor function. Last year Cuervo collaborated with Sheng Zhang, a professor at The University of Texas Health Science Center at Houston on experiments showing that huntingtin—the Huntington's disease protein—helps the cell's autophagy system identify what it should eliminate. Researchers had focused so much on huntingtin's toxicity that it was surprising to discover this molecule has a regular day job, Cuervo notes. Rather than being the bad

guy that ties up the cleaning system, huntingtin "also happens to be part of the cleaning crew," she says. "That changes the way we have to approach the problem."

In recent years Cuervo and co-workers have discovered that giving the cleaning crew a little boost can go a long way. The tough part is figuring out which parts to tweak. "There are many ways to clean the house—a vacuum, a broom," Cuervo says. Similarly, in cells "there are many ways to bring proteins to the lysosome." Lysosomes are the final destination for misshapen proteins that get degraded in the autophagy system. One type of autophagy traps chunks of cellular material into "bags" that fuse with lysosomes. A different branch of autophagy—a specialty of Cuervo's lab—involves molecular chaperones that escort misbehaving proteins through special tunnels into the lysosome.

Several years ago her team designed a chemical that helps cells produce more tunnel components. When tested in cultured cells, the compound specifically activated chaperone-mediated autophagy without touching other pathways. More importantly, in recent studies yet to be published the chemical appears to improve anxiety, depression and memory in mice that mimic some features of Alzheimer's. The researchers also plan to test the compound in mice modeling Parkinson's disease.

Tampering with chaperones can be tricky, though. Sometimes chaperones hang onto a bad protein for too long. The major chaperones are not very discriminating. They recognize all unfolded proteins—"anything that's disordered or stretched out"—and cover those exposed, sticky regions to prevent clumping, says neuroscientist Chad Dickey of the University of South Florida. So it is easy for chaperones to get confused with tau, a protein that accumulates in the brains of people with Alzheimer's. Normally tau binds to microtubules—molecular conveyor belts that move chromosomes and vesicles within cells. In the early stages of the disease, however, tau proteins undergo changes that nudge them off microtubules. Because tau has a loose molecular structure, chaperones treat free-floating tau as a misfolded protein. They hold onto it, trying to put it back onto microtubules, rather than sending it for degradation. As a result, tau accumulates inside cells to form the infamous clumps that are considered hallmark pathology in neurodegenerative disorders such as Alzheimer's and progressive supranuclear palsy.

Once a protein lands with a chaperone, any of a number of molecular co-factors swoop in to decide the protein's fate. In separate studies published in June research teams identified two chaperone complexes that appear to work by ushering disease-linked proteins out of cells. The Florida group identified a co-factor that hooks up with tau, alpha-synuclein and other disease-associated molecules to evict them. "We think it's a last-ditch effort by neurons to get rid of bad proteins," Dickey says. Meanwhile a team led by Yihong Ye, a cell biologist at the National Institutes of Health, discovered another pathway that uses different protein workhorses to accomplish a similar off-load. The latter mechanism seems to only dispatch alpha-synuclein whereas the other system can dump several neurodegenerative disease–associated proteins.

The scientists are not sure if the newly discovered pathways are connected or if they relate to a previously identified system that helps clear amyloid beta and other toxins out of the brain. Still, researchers are intrigued by the possibility that cells may use these clearance mechanisms to propagate misfolded proteins throughout the brain—in which case targeting the mechanisms could conceivably slow disease progression.

Compounds that target autophagy or inhibit chaperones have been tested in many clinical trials, mostly in cancer patients. Cancer was the first disease researchers connected with autophagy. Generally scientists have thought autophagy protects against cancer, although some evidence suggests it can help tumor cells cope with nutrient scarcity and other stresses. Because the impact of autophagy on cancer seems to go both ways, cancer trials have tested therapies that enhance autophagy as well as drugs that block it. For neurodegenerative diseases, such research is still in its early phase. One problem is that many of the experimental molecules are too big to enter the brain, Dickey says. Another challenge: the drugs are not very selective. They may influence other processes within the cell.

Nevertheless several autophagy-enhancing compounds have entered human testing for treatment of brain disorders. One, rilmenidine, is a prescription medicine for treating high blood pressure. Recently scientists completed a safety trial of rilmenidine in 16 U.K. adults with early Huntington's disease. Data analyses are ongoing, says University of Cambridge molecular geneticist David Rubinsztein, one of the trial

investigators. Bioblast Pharma—an Israel-based biotech company focused on rare diseases—is launching a phase I trial of trehalose, a sugar found in plants, fungi and invertebrates. The study will enroll healthy volunteers to receive the autophagy-inducing compound intravenously. Last month researchers led by Thomas Kukar, a professor at Emory University, published a paper showing that trehalose can reverse lysosomal deficiencies in mouse models of frontotemporal dementia. And Duff's lab has unpublished data suggesting that trehalose lessens tau pathology and improves behavior in mouse models of neurodegeneration.

"It seems you just want to clear out all the garbage in the brain," Duff says.

ABOUT THE AUTHOR(S)

Esther Landhuis

Esther Landhuis is a freelance science journalist in the San Francisco Bay Area.