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SECRETS OF THE CELL

Self-Destructive Behavior in Cells May Hold Key to a Longer Life

By CARL ZIMMER

Deep down, we are all cannibals. Our cells are perpetually devouring themselves, shredding their own complex molecules to pieces and recycling them for new parts. Many of the details of our endless self-destruction have come to light only in the past few years. And to the surprise of many scientists, links are now emerging between this inner cannibalism and diseases like Alzheimer's disease and cancer.

"There's been an explosion," said Daniel Klionsky of the University of Michigan. "All of a sudden, researchers in different fields are seeing a connection."

In fact, as Dr. Klionsky wrote in a paper published online in Trends in Cell Biology, this cannibalism may extend our lifespan. Increasing our body's ability to self-destruct may, paradoxically, let us live longer.

Our cells build two kinds of recycling factories. One kind, known as the proteasome, is a tiny cluster of proteins. It slurps up individual proteins like a child sucking a piece of spaghetti. Once inside the proteasome, the protein is chopped up into its building blocks.

For bigger demolition jobs, our cells rely on a bigger factory: a giant bubble packed with toxic enzymes, known as a lysosome. Lysosomes can destroy big structures, like mitochondria, the sausage-shaped sacs in cells that generate fuel. To devour a mitochondrion, a cell first swaddles it in a shroudlike membrane, which is then transported to a lysosome. The shroud merges seamlessly into the lysosome, which then rips the mitochondrion apart. Its remains are spit back out through channels on the lysosome's surface.

Lysosomes are versatile garbage disposals. In addition to taking in shrouded material, they can also pull in individual proteins through special portals on their surface. Lysosomes can even extend a mouthlike projection from their membrane and chew off pieces of a cell.

The shredded debris that streams out of the lysosomes is not useless waste. A cell uses the

material to build new molecules, gradually recreating itself from old parts. “Every three days, you basically have a new heart,” said Dr. Ana Maria Cuervo, a molecular biologist at Albert Einstein College of Medicine.

This self-destruction may seem like a reckless waste of time and energy. Yet it is essential for our survival, and in many different ways. Proteasomes destroy certain proteins quickly, allowing them to survive for only about half an hour. That speed allows cells to keep tight control over the concentrations of the proteins. By tweaking the rate of destruction, it can swiftly raise or lower the number of any kind of protein.

Lysosomes, which eat more slowly than proteasomes, serve different roles that are no less essential. They allow cells to continue to build new molecules even when they are not getting a steady supply of raw ingredients from the food we eat. Lysosomes also devour oily droplets and stores of starch, releasing energy that cells can use to power the construction of new molecules.

“If you don’t have a snack between lunch and dinner,” Dr. Cuervo said, “you’re going to have to activate your lysosomes to get nutrients.”

Lysosomes become even more active if dinner never comes, and a short-term hunger turns to long-term starvation. Cells respond to famine by making only a small number of crucial molecules and using lysosomes to destroy the rest. “When times are good, make everything,” Dr. Klionsky said. “When times are lean, focus on what you need. You can get rid of everything else.”

This strategy for survival, known as autophagy (“eating oneself”), evolved in our ancestors over two billion years ago. Today, all animals rely on it to endure famines, as do plants, fungi and single-cell protozoa.

Autophagy’s great antiquity has helped scientists discover the genes that make it possible in humans. Rather than study starving people, they introduced mutations into yeast and then observed which strains could no longer survive without food. In many cases, the scientists discovered, the mutations that made yeast vulnerable struck genes that are involved in autophagy. They were then able to find nearly identical versions of those genes in the human genome.

The protection humans get from lysosomes is essential not just during famines. It is also vital just after birth. When babies emerge from their mothers, they need huge amounts of energy so that they can start to run their bodies on their own. But this demand comes at precisely the moment that babies stop getting food through their umbilical cord. Japanese scientists have found that lysosomes in mice kick into high gear as soon as they are born. After a day or two, as they start to nurse, the rate of autophagy drops back to normal.

When the scientists engineered mice so they could not use their lysosomes at birth, the newborn mice almost immediately died of starvation.

Even if you enjoy a steady supply of food your entire life, you still rely on autophagy for another reason: to keep the molecules in your cells in good working order. Cells make a lot of defective molecules. They misread genes, for example, and misfold proteins. Even a perfectly crafted molecule does not stay perfect for long. “Proteins go bad with time,” Dr. Klionsky said. “They age, and they wear out.”

When proteins and other molecules go bad, they can start to gum up the intricate chemical reactions on which a cell’s survival depends. The cell recognizes defective parts and tags them for destruction. Experiments on flies show the harm that can occur when cells cannot clear away the old and bring in the new. Flies that are genetically engineered with defective lysosomes start to accumulate abnormal clumps of proteins in their cells. The clumps build up especially in their neurons, which start to die as a result.

The Belgian biochemist Christian de Duve discovered lysosomes in 1955, for which he later won the Nobel Prize. In 1963, scientists discovered that a genetic defect in lysosomes was responsible for a disorder known as Pompe disease, which weakens the heart and muscles. Those who have the disease are missing a protein that lysosomes need to break down stores of energy. Today over 50 disorders are recognized as the result of one defect or another in lysosomes. Doctors can now treat some of these diseases by supplying people with the proteins they lack.

In recent years, scientists have also found evidence of autophagy in preventing a much wider range of diseases. Many disorders, like Alzheimer’s disease, are the result of certain kinds of proteins forming clumps. Lysosomes can devour these clumps before they cause damage, slowing the onset of diseases.

Lysosomes may also protect against cancer. As mitochondria get old, they cast off charged molecules that can wreak havoc in a cell and lead to potentially cancerous mutations. By gobbling up defective mitochondria, lysosomes may make cells less likely to damage their DNA. Many scientists suspect it is no coincidence that breast cancer cells are often missing autophagy-related genes. The genes may have been deleted by mistake as a breast cell divided. Unable to clear away defective mitochondria, the cell’s descendants become more vulnerable to mutations.

Unfortunately, as we get older, our cells lose their cannibalistic prowess. The decline of autophagy may be an important factor in the rise of cancer, Alzheimer’s disease and other disorders that become common in old age. Unable to clear away the cellular garbage, our bodies start to fail.

If this hypothesis turns out to be right, then it may be possible to slow the aging process by raising autophagy. It has long been known, for example, that animals that are put on a strict low-

calorie diet can live much longer than animals that eat all they can. Recent research has shown that caloric restriction raises autophagy in animals and keeps it high. The animals seem to be responding to their low-calorie diet by feeding on their own cells, as they do during famines. In the process, their cells may also be clearing away more defective molecules, so that the animals age more slowly.

Some scientists are investigating how to manipulate autophagy directly. Dr. Cuervo and her colleagues, for example, have observed that in the livers of old mice, lysosomes produce fewer portals on their surface for taking in defective proteins. So they engineered mice to produce lysosomes with more portals. They found that the altered lysosomes of the old experimental mice could clear away more defective proteins. This change allowed the livers to work better.

“These mice were like 80-year-old people, but their livers were functioning as if they were 20,” Dr. Cuervo said. “We were very happy about that.”

Andrea Ballabio, the scientific director of Telethon Institute of Genetics and Medicine in Naples, Italy, and his colleagues have found another way to raise autophagy. By studying the activity of genes that build lysosomes, they discovered that at least 68 of the genes are switched on by a single master protein, known as TFEB.

When Dr. Ballabio and his colleagues engineered cells to make extra TFEB, the cells made more lysosomes. And each of those lysosomes became more efficient. The scientists injected the cells with huntingtin, a protein that clumps to cause the fatal brain disorder Huntington’s disease. The cells did a much better job of destroying the huntingtin than normal cells.

“This is a very good sign,” Dr. Ballabio said. “We’re very excited because this network of genes may apply to a number of diseases.”

Dr. Ballabio and other researchers are now investigating ways in which they can increase autophagy with drugs or diets — raising the number of portals on lysosomes, for example, or causing cells to make extra TFEB. But developing such treatments will require a sophisticated understanding of autophagy. After all, autophagy is a potent force for destruction, and if lysosomes are accidentally ripped open, their toxic enzymes can kill a cell.

As Dr. Klionsky, of the University of Michigan, said, “You can’t just turn this on and let it go.”

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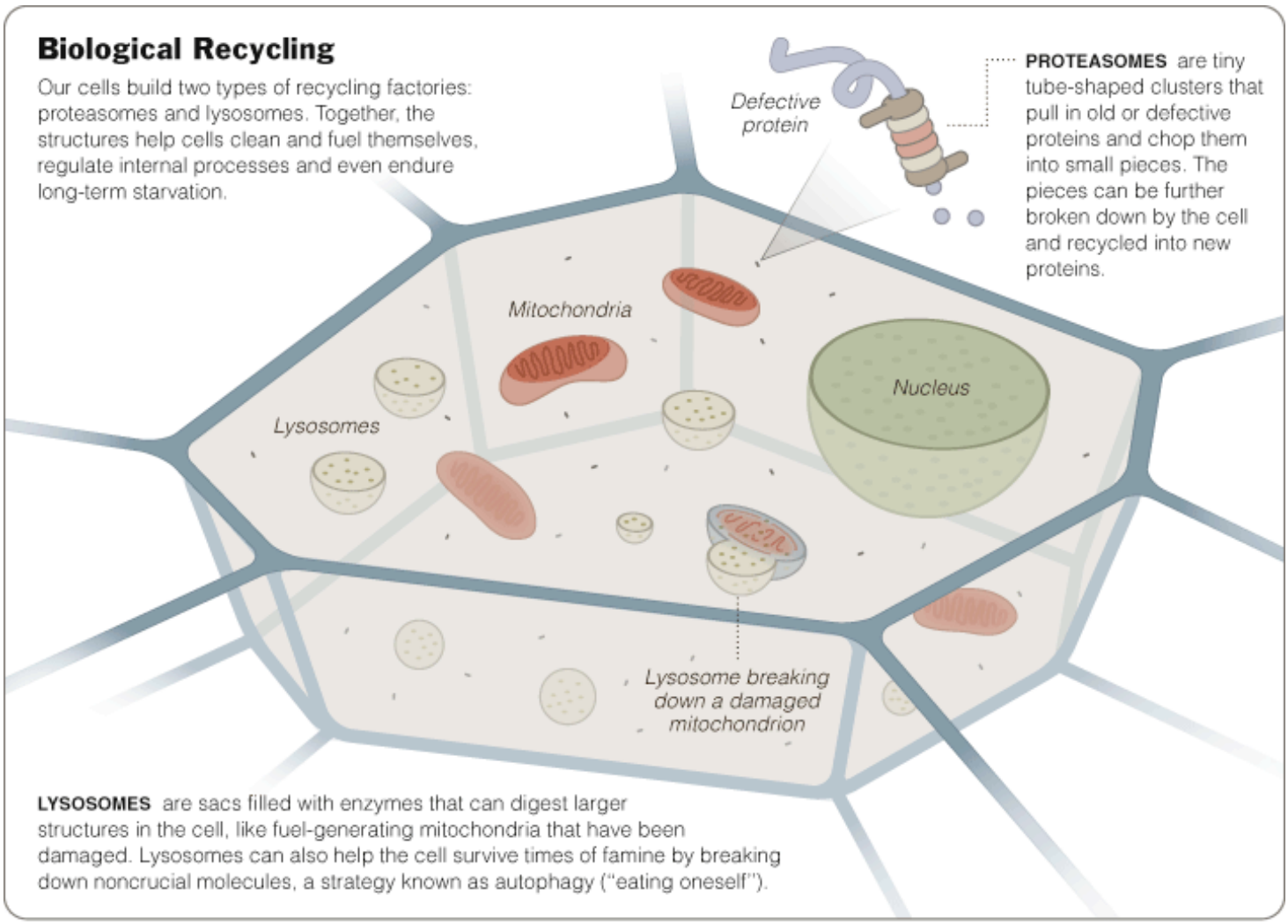

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