Autophagy: Is It Cancer’s Friend or Foe?

Cells rely on autophagy to recycle their components, and much evidence favors the idea that this “self-eating” suppresses tumor development. But other data suggest that autophagy fosters tumor development and actually protects cancer cells from treatments.

Environmentalists have long proclaimed the importance of recycling. Now cell biologists are delivering a similar message. Within the past few years, they have been working out the genetic and biochemical underpinnings of a cellular recycling system known as autophagy, and what they are learning could shed light on a variety of diseases—cancer among them.

Autophagy has long been known for its roles in protecting cells against stresses such as starvation and in eliminating defective cellular constituents, including subcellular structures such as the energy-generating mitochondria. It is essentially a form of self-cannibalism—hence the name, which means “eating oneself”—in which the cell breaks down its own components. Cells can then recycle the resulting degradation products, using them to provide the energy and building blocks necessary for their survival (Science, 5 November 2004, p. 990).

The cancer connection, which has cropped up more recently, comes from several research teams that have found that autophagy appears to suppress tumor development in animals. This includes demonstrations that some tumor-suppressor genes stimulate autophagy and that certain cancer-causing oncogenes inhibit it. But although such work suggests that boosting autophagy will prevent or treat cancers, “the situation is not so clear,” cautions Patrice Codogno of the University of Paris-Sud in France.

Indeed, researchers continue to wrestle with the crucial question of whether some tumors exploit autophagy in order to survive. The process is known to kick in when cells encounter nutrient shortages. And because cancer cells in a growing tumor can find themselves short of needed nutrients, inducing autophagy could give them a hand. There’s also evidence that in some cases autophagy helps cancer cells fight off chemotherapeutic drugs, although in others it may be part of the drugs’ killing mechanisms. “There’s controversy about whether one should be turning autophagy on or off to treat cancer,” says Beth Levine of the University of Texas Southwestern Medical Center in Dallas.

Early neglect

Suspicion that autophagy plays a role in cancer first arose about 3 decades ago when researchers noted that cancer cells seemed deficient in the process compared to normal cells. They made this determination either by measuring the rates of degradation of long-lived proteins or by looking for the characteristic double-membraned vacuoles that form in cells undergoing autophagy. These vacuoles encircle the cellular cargo destined for degradation and then fuse with lysosomes, which carry a host of enzymes for digesting proteins and other materials.

At the time, however, researchers couldn’t do much with the cancer connection, mainly because the genes involved in autophagy hadn’t been identified. The early work implicating autophagy defects was “largely ignored by the cancer community because the evidence was mainly correlational,” recalls Levine.

That didn’t change until the early 1990s when yeast researchers, particularly Yoshinori Ohsumi of the National Institute for Basic Biology in Okazaki, Japan, Daniel Klionsky of the University of Michigan, Ann Arbor, and Michael Thumm of Georg-August University in Göttingen, Germany, began teasing out the genes needed for autophagy in that simple eukaryote. So far, more than 20 yeast autophagy genes have been unearthed, several of which have counterparts in mammals.

Levine, who didn’t set out to study autophagy, identified one such counterpart in 1998, helping to spark the current wave of interest in autophagy’s role in cancer. Her team found the gene, now called beclin-1, while screening for binding partners for the protein encoded by the mouse bcl-2 oncogene. The sequence of the new gene, which also occurs in humans, resembled that of the yeast autophagy gene 6 (ATG6), and the Dallas group showed that beclin-1 could repair the autophagy defect in yeast with no ATG6 activity.

Even more interestingly, Levine and her colleagues noted that the human gene maps to a chromosomal location that’s frequently deleted in ovarian, breast, and prostate cancers—an indication that the site harbors a tumor-suppressor gene. The Levine team also found that beclin-1 expression is much reduced in invasive breast cancer cells compared to normal cells.

Unlike most tumor suppressors, only one copy of the cell’s two beclin-1 genes is usually lost in breast cancer. So Levine and her colleagues recreated this situation by knocking out a single copy of the gene in mice. The resulting animals showed both a decrease in autophagy and an increased frequency of cancers of the lungs and liver as well as lymphomas, the team reported in the December 2003 Journal of Clinical Investigation. The mice also developed benign breast tumors.

A team led by Arnold Levine (not related to Beth Levine) of the University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School in New Brunswick and Nathaniel Heintz of Rockefeller University in New York City reported similar results the same month in the Proceedings of the National Academy of Sciences. That “pinpoints that beclin-1 is a tumor suppressor,” says team member Shengkan Jin of the Robert Wood Johnson Piscataway campus.

Other researchers have connected previously identified tumor-suppressor genes to...
autophagy regulation. Codogno’s team showed that one of these is PTEN, which inhibits a major cell growth stimulatory pathway and, as a result of that, a protein called TOR. Because TOR normally curbs autophagy by inhibiting TOR. And Adi Kimchi and her colleagues at the Weizmann Institute of Science in Rehovot, Israel, have found that the tumor suppressor known as DAPK (for death-associated protein kinase) is yet another autophagy stimulator.

Conversely, many oncogenes appear to inhibit autophagy. Codogno and his colleagues have found that overactivity of the oncogene AKT curbs autophagy—the expected result because it promotes TOR activity. And last month in Washington, D.C., at the annual meeting of the American Association for Cancer Research (AACR), John Cleveland of St. Jude Children’s Research Hospital in Memphis, Tennessee, presented as-yet- unpublished data from his lab indicating that the carcinogenic effects of the well-known myc oncogene are at least partly due to its ability to decrease autophagy. The evidence, obtained in collaboration with Michael Kastan, also at St. Jude, includes the finding that myc activity suppresses the expression of ATG genes 8 and 9. “Oncogenes suppress autophagy during tumor development,” Cleveland concludes.

Then there’s bcl-2, the gene that helped Beth Levine and her colleagues identify beclin-1. This oncogene promotes the survival of cancer cells by inhibiting apoptosis, a process by which dysfunctional cells kill themselves. Evidence published by Levine and her colleagues last September in Cell raises the possibility that bcl-2 prevents autophagic cell death as well. Although autophagy is often protective, it can kill cells in some circumstances; they essentially digest themselves to death.

The researchers showed that binding of the Bcl-2 protein to the protein product of beclin-1 inhibits autophagy. Levine suggests that this suppression by Bcl-2 helps keep autophagy in check under normal conditions. But if bcl-2 activity is excessive, as it is in some cancers, the consequent suppression of autophagy could allow damaged cells to complete a cancerous transformation.

Killing normal cells is not the only way that autophagy could protect against tumor development, however. Autophagy’s recycling ability can eliminate damaged cell components, especially organelles such as the mitochondria. Indeed, Khionsky says, it “is virtually the only way to get rid of whole organelles.” Getting rid of defective mitochondria, which release abnormally large amounts of DNA-damaging reactive oxygen species, could help protect cells against cancer-causing mutations, Jin and others suggest.

Heart of the controversy

Although many cancer therapies are thought to kill tumor cells by inducing apoptosis, researchers have begun to find signs of autophagy in tumor cells exposed to chemotherapy or radiation. The chemotherapeutic drugs that appear to trigger autophagy include tamoxifen, rapamycin, and arsenic compounds. “Many treatments induce autophagy rather than apoptosis,” says Seiji Kondo of M. D. Anderson Cancer Center in Houston, Texas.

The crucial question, however, is whether autophagy helps kill tumor cells or instead protects them from the therapies’ cell-damaging effects. There’s evidence on both sides.

One example favoring a cancer-killing role for autophagy involves the chemotherapeutic drug rapamycin, which is a known TOR inhibitor. Kondo and his colleagues have found that the rapamycin sensitivity of cells derived from highly malignant brain tumors called gliomas correlates with the drug’s ability to induce autophagy. The researchers also found that drugs that increase autophagy boost rapamycin’s ability to kill glioma cells.

In contrast, at the AACR meeting, Ravi Amaravadi, who works in Craig Thompson’s lab at the University of Pennsylvania, presented results supporting the idea that autophagy can protect against a chemotherapeutic drug. This work involved genetically engineered mice that overexpress the myc oncogene and develop lymphomas as a result. The animals also carried an altered p53 gene that can be activated by treatment with tamoxifen. The resulting p53 activity induces apoptosis, leading to a temporary regression of the animals’ lymphomas.

The Pennsylvania team showed that chloroquine, a drug that previous studies had suggested was an autophagy inhibitor, enhanced the animals’ responses to tamoxifen treatment. “Cancer cells, when faced with cytotoxic damage [from chemotherapy], turn to autophagy. It’s a mechanism that cancer cells adopt to survive,” Thompson maintains.

This situation is complicated by results Cleveland described in his AACR talk. His team found that chloroquine can suppress myc-induced lymphoma development in mice. But Cleveland and his colleagues also concluded that chloroquine is an autophagy inducer, not an inhibitor. So although their mouse results were similar, the two groups came to diametrically opposite interpretations about whether autophagy enables chemotherapies to kill cancer cells or instead protects them from the drugs.

The answer to the question of whether inducers of autophagy will be good or bad for cancer therapies may vary depending on the nature of the cancer, the drug, or both. The drug temozolomide (TMZ), which is currently in clinical trials for treating gliomas, provides an illustration of this kind of complexity. Kondo’s team found that a drug that inhibits the early stages of autophagy enhanced TMZ’s antitumor effects, whereas a different drug that blocks an early stage of autophagy suppressed them. “We have to understand all the players to predict whether a therapy [promoting autophagy] will protect the cells or kill them,” Kimchi says. Obviously, autophagy researchers still have their work cut out for them.

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