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# New research shows that autophagy can operate in cell nucleus to guard against start of cancer

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Autophagy, literally self-eating or the degradation of unwanted cellular bits and pieces by the cell itself, has been shown for the first time to also work in the cell nucleus. In addition, in this setting it plays a role in guarding against the start of cancer, according to new research from the Perelman School of Medicine at the University of Pennsylvania.

Autophagy is closely linked to many human diseases. This is due in part to its role in digesting the unfavorable material in cells that has the potential to cause problems. By removing this "junk" in cells, autophagy serves as the garbage disposal and recycling system to keep bodies healthy.

Dysfunctional autophagy, on the other hand, is implicated in aging and a range of diseases including cancer, neurodegenerative diseases, muscular disorders, diabetes, and obesity. Manipulation of autophagy is actively being pursued as a potential druggable pathway to treat many of these disorders, some of which are in clinical trials.

The material that autophagy can digest ranges from a single molecule to a whole bacterium. Previously, all known substances consumed by autophagy took place outside the nucleus in the cell's cytoplasm.

In the study published today in Nature, autophagy is shown, for the first time, to digest nuclear material in mammalian cells. "We found that the molecular machinery of autophagy guides the degradation of components of the nuclear lamina in mammals," said senior author Shelley Berger, PhD, the Daniel S. Och University Professor in the departments of Cell & Developmental Biology, Genetics, and Biology. Berger is also founding director of the Penn Epigenetics Program.

The nuclear lamina is a network of protein filaments lining the inside of the membrane of the nucleus. It is a crucial network in the nucleus, providing mechanical support to the nucleus and also regulating gene expression by making some areas of the genome less or more available to be transcribed into messenger RNA.

On the autophagy side of this complicated machinery, a key protein called LC3 was detected in the nucleus in earlier studies. But the nuclear location of an autophagy protein thought to be functional in the cytoplasm begged the question: why is LC3 in the nucleus in the first place?

First author and postdoctoral fellow Zhixun Dou, PhD, an experienced researcher in autophagy, came to the Berger lab with this question in mind. At the same time, coauthor Peter Adams, from the University of Glasgow, published a previous study on the breakdown of the nuclear lamina in which he observed a peculiar protrusion, or blebbing, of the nuclear envelope into the cytoplasm, and these blebs contained DNA, nuclear lamina proteins, and chromatin (the nuclear structures in which genes reside). This evidence led the Berger and Adams labs to work together to find out what was going on.

Using sophisticated biochemical and sequencing methods, Dou found that laminB1, a key component of the nuclear lamina, and LC3 were contacting each other in same places on chromatin. In fact, in unanticipated findings, LC3 and laminB1 are physically bound to each other. LC3 directly interacts with lamin B1 and binds to lamin-associated domains on chromatin.

Autophagy in Cancer and Aging

In response to cellular stress that can cause cancer, the team found that LC3, chromatin, and laminB1 migrate from the nucleus -- via the nuclear blebs -- into the cytoplasm and are eventually targeted for disposal. This breakdown of laminB1 and other nuclear material leads to a cellular state called senescence, or literally "getting old." The Berger and Adams labs have been studying senescence in conjunction with cancer for quite some time. Human cells have complicated ways to protect themselves from becoming cancerous, and one way is to drive themselves to become old through senescence, so that the cells can no longer replicate.

The team showed that when a cell's DNA is damaged or an oncogene is activated (both of which can cause cancer), a normal cell triggers the digestion of nuclear lamina by autophagy, which promotes senescence. Inhibiting this digestion of nuclear material weakens the senescence program and leads to cancerous growth of cells.

"The nucleus is the headquarters of a cell," Dou said. "When a cell receives a danger alarm, amazingly, it deliberately messes up its headquarters, with the consequence that many functions are completely stopped for the cell. Our study suggests this new function of autophagy as a guarding mechanism that protects cells from becoming cancerous."
Although senescence suppresses cancer, which is the good side of this physiological balance, there is also a dark side. Senescence is associated with normal aging, and senescent cells accumulate in aged tissues, which impair the normal functions of the tissue and contribute to age-related diseases.

The team noted that while autophagy digestion of the nucleus is able to restrain cancer, this machinery is improperly turned on during normal aging. "There is a short term 'tactical' advantage, but a long term 'strategic' defeat," Berger explains. "This mechanism makes a normal cell, even without cancer stress, get old much faster, and in a detrimental way."

In support of this notion, the team found that in late middle-aged normal cells, blocking the autophagy-driven breakdown of the nuclear lamina can make cells live 60 percent longer. In fact, say the researchers, the age extension is equivalent to a 70-year-old person living to over 110 years old.

Looking toward the future, the team reasons that specific manipulation of the nuclear digestion by autophagy holds promise to intervene in age-related diseases. The team showed that a blocking peptide, which inhibits LC3-laminB1 interaction, is able to slow cell aging. The implications are that a small molecule could be made to stop the long-term dark side of the senescence pathway, and to treat age-related diseases, especially those related to chronic inflammation as seen in human aging. Such a molecule might also be able to ameliorate the side effects of chemotherapy or radiation therapy of cancer patients. Dou and Berger are actively pursuing this direction.

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