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**New Strategy For Stimulating Autophagy**

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## **Abstract:**

Autophagy has become a hot topic in recent years, earning its discoverer the Nobel Prize in Physiology and Medicine in 2016. The process involves the rounding up of misfolded proteins and obsolete organelles within a cell into vesicles called autophagosomes. The autophagosomes then fuse with a lysosome, an enzyme-containing organelle that breaks down those cellular macromolecules and converts it into components the cell can re-use.

## **Introduction:**

Autophagy is a process in which long-lived proteins, damaged cell organelles, and other cellular particles are sequestered and degraded. This process is important for maintaining the cellular microenvironment when the cell is under stress.

Autophagy plays a direct or indirect role in health and disease. A simplified definition of autophagy is that it is an exceedingly complex process which degrades modified, superfluous (surplus) or damaged cellular macromolecules and whole organelles using hydrolytic enzymes in the lysosomes. It consists of sequential steps of induction of autophagy, formation of autophagosome precursor, formation of autophagosome, fusion between autophagosome and lysosome, degradation of cargo contents, efflux transportation of degraded products to the cytoplasm, and lysosome reformation.

One characteristic of aging is the accumulation of damage, and this is largely due to the failure of autophagy to attain normal functional levels. It can be seen that bringing levels of autophagy to youthful levels can ameliorate aging by clearing out damaged parts of the cell<sup>1</sup>.

## **Discussion :**

Brown University researchers studying the biology of aging have demonstrated a new strategy for stimulating autophagy, the process by which cells rebuild themselves by recycling their own worn-out parts.

In a study published in the journal *Cell Reports*, the researchers show that the approach increased the lifespans of worms and flies, and experiments in human cells hint that the strategy could be useful in future treatments for Alzheimer's disease, ALS and other age-related neurodegenerative conditions.

"Autophagy dysfunction is present across a range of age-related diseases including neurodegeneration, Autophagy has become a hot topic in recent years, earning its discoverer the Nobel Prize in Physiology and Medicine in 2016. The process involves the rounding up of misfolded proteins and obsolete organelles within a cell into vesicles called autophagosomes. The autophagosomes then fuse with a lysosome, an enzyme-containing organelle that breaks down those cellular macromolecules and converts it into components the cell can re-use.

The study aim is if can increase the number of autophagy by manipulating a transcription factor (a protein that turns gene expression on and off) that regulates autophagic activity. In order for the transcription factor to switch autophagic activity on, it needs to be localized in the nucleus of a cell. So Lapierre and his team screened for genes that enhance the level of the autophagy transcription factor, known as TFEB, within nuclei.

Using the nematode *C. elegans*, the screen found that reducing the expression of a protein called XPO1, which transports proteins out of the nucleus, leads to nuclear accumulation of the nematode version of TFEB. That accumulation was associated with an increase in markers of autophagy, including increased autophagosome, autolysosomes as well as increased lysosome biogenesis. There was also a marked increase in lifespan among the treated nematodes of between about 15 and 45 percent.

"What showed was that by blocking the escape of this transcription factor from the nucleus, we could not only influence autophagy but we could get an increase in lifespan as well.

Study identifies critical role of protein in sperm tail development

Essential fats in diet may regulate protein secretion in muscles by altering gene expression

Study: Different strains of same protein may contribute to different Parkinson's-related brain disorders

The next step was to see if there were drugs that could mimic the effect of the gene inhibition used in the screening experiment. The researchers found that selective inhibitors of nuclear export (SINE), originally developed to inhibit XPO1 to treat cancers, had a similar effect -- increasing markers of autophagy and significantly increasing lifespan in nematodes.

The researchers then tested SINE on a genetically modified fruit fly that serves as a model organism for the neurodegenerative disease ALS. Those experiments showed a small but significant increase in the lifespans of the treated flies. "Our data suggests that these compounds can alleviate some of the neurodegeneration in these flies," .As a final step, the researchers set out to see if XPO1 inhibition had similar effects on autophagy in human cells as it had in the nematodes. After treating a culture of human HeLa cells with SINE, the researchers found that, indeed, TFEB concentrations in nuclei increased, as did markers of autophagic activity and lysosomal biogenesis.

" studies tell us that the regulation of the intracellular partitioning of TFEB is conserved from nematodes to humans and that SINE could stimulate autophagy in humans," . "SINE have been recently shown in clinical trials for cancer to be tolerated, so the potential for using SINE to treat other age-related diseases is there.

Future research will focus on testing these drugs in more clinically relevant models of neurodegenerative diseases. But this initial research is a proof of concept for this strategy as a means to increase autophagy and potentially treat age-related diseases<sup>2</sup>.

### **Result:**

Autophagy makes us more efficient machines to get rid of faulty parts, stop cancerous growths, and stop metabolic dysfunction like obesity and diabetes, and it is the key of slowing the ageing process <sup>2</sup>

**Conclusion:**

Autophagy allows the orderly degradation and recycling of cellular components.

In macroautophagy, targeted cytoplasmic constituents are isolated from the rest of the cell within a double-membraned vesicle known as an autophagosome.

The autophagosome eventually fuses with lysosomes and the contents are degraded and recycled.

**References:**

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