Autophagy Suppresses Spontaneous Tumor Formation

WHILE ALL COMPONENTS of our bodies are constitutively synthesized, they are also constitutively degraded or eliminated. Whole organisms and even individual cells can maintain their function and freshness through recycling their own constituents (e.g. proteins and organelles) and can adapt to various internal and external changes.

Macroautophagy, which is usually called "autophagy", is one of the major degradation pathways in the cell along with the ubiquitin-proteasome system. In autophagy, intracellular components are sequestered by autophagosomes and then degraded upon fusion with lysosomes. Using autophagosome-indicator mice (GFP-LC3 transgenic mice) and conventional *ATG5* knockout mice, we have shown that autophagy is up-regulated during starvation and is critically important for maintenance of the amino acid pool. Autophagy is also essential for preimplantation development as the amino acid supplying system and for intracellular protein quality control, which has been suggested by studies using oocyte- and neural cell-specific *ATG5* knockout mice, respectively. Furthermore, autophagy is important for differentiation of erythroblasts and adipocites, elimination of intracellular microbes, and presentation of cytoplasmic antigens.

However, the long-term effect of defects in autophagy *in vivo* has never been systematically analyzed. Evidence using cell culture and allografted tumor models has suggested that autophagy is also involved in tumor suppression. However, results from currently available *in vivo* models have been limited. Because systemic deletion of autophagy genes causes embryonic or neonatal lethality, the role of autophagy in tumor suppression has never been tested *in vivo*.

To overcome these limitations, we generated mice with systemic mosaic deletion of *ATG5*, in which only a small population of cells were autophagy-defective in every tissue. These mice are viable for more than 19 months and develop multiple benign tumors only in the liver. Swollen mitochondria and oxidative stress and genomic damage responses were detected in the hepatic tumor cells. Liver-specific *ATG7* deficient mice also developed liver tumors, but their size was reduced by concomitant knockout of the *p62* gene (collaboration with Dr. Masaaki Komatsu, Tokyo Metropolitan Institute of Medical Science). Our study suggests that continuous autophagy is important for prevention of accumulation of abnormal mitochondria and *p62*, and thereby for suppression of spontaneous tumorigenesis particularly in the liver.

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While we have shown that autophagy can be a tumor suppressor, other studies have also suggested that autophagy could support tumor progression and survival. In fact, tumor cell death can be induced by autophagy-inhibiting drugs such as hydroxychloroquine in combination with conventional chemotherapy, and clinical trials of autophagy-inhibiting drugs have begun in the United States. These two apparently opposed roles of autophagy are not mutually exclusive; generation of only benign tumors, not cancers, in our models suggests that autophagy may be required for progression beyond the benign state. This study also provides a novel tool to study autophagy in a non-biased way. Since autophagy is likely involved in a variety of physiological and pathological processes, the *ATG5* mosaic mice would be useful to explore novel roles of autophagy.

References

Takamura, A., Komatsu, M., Hara, T., Sakamoto, A., Kishi, C., Waguri, S., Eishi, Y., Hino, O., Tanaka, K., Mizushima, N. Autophagy-deficient mice develop multiple liver tumors. *Genes Dev*. 25: 795-800 (2011).
Mizushima, N., Komatsu, M. Autophagy: renovation of cells and tissues. *Cell*. 147:728-41 (2011).

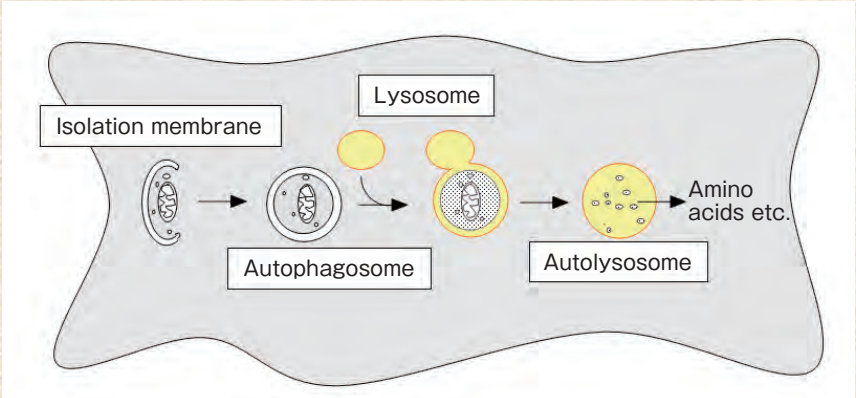

Fig.1: **The process of autophagy.**
A portion of cytoplasm, including organelles, is enclosed by an autophagosome. The outer membrane of the autophagosome fuses with the lysosome, and the internal material is degraded.

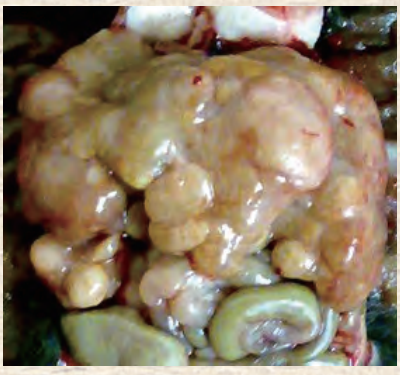

Fig.2:
Tumors formed in *ATG5* mosaically deleted mice.
Liver tumors are formed in mice with mosaic deletion of the *ATG5* gene (at 19 months).