FUNDING PROGRAM FOR NEXT GENERATION WORLD-LEADING RESEARCHERS

Project Title: In-depth analysis of autophagy in health and disease	
Name: Masaaki KOMATSU	**Institution**: Tokyo Metropolitan Institute of Medical Science

1. Background of research

Autophagy is a cellular degradation system in which cytoplasmic components including organelles are sequestered by double membrane structures called autophagosomes and sequestered materials are degraded by lysosomal hydrolases for supply of amino acids and for cellular homeostasis. The autophagy induced in response to nutrient deprivation is executed in a non-selective fashion, and adaptation to nutrient-poor conditions is the main purpose of autophagy. On the other hand, recent studies have shed light on another indispensable role for starvation-independent or constitutive autophagy in cellular homeostasis, which is mediated by selective degradation of specific substrate(s).

2. Research objectives

In this research program, we aim to clarify the pathophysiological roles of selective autophagy as well as the molecular mechanisms.

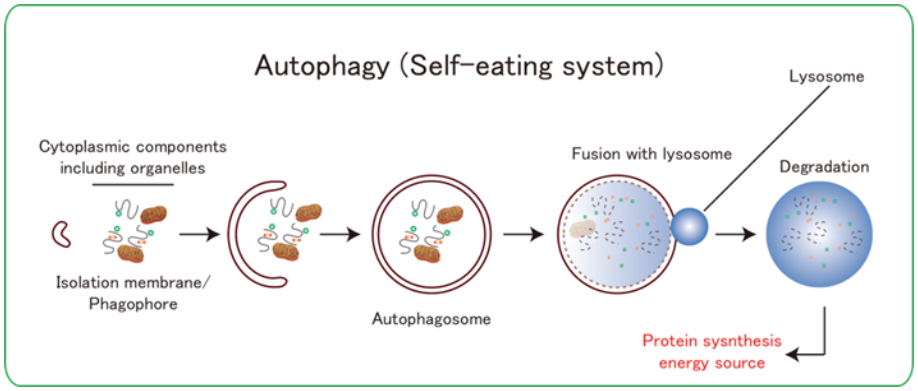
3. Research characteristics (incl. originality and creativity)

Based on our strong expertise in protein biochemistry and mouse genetic study, we relentlessly pursue a revolutionary approach to the understanding of the role of selective autophagy in suppression of tissue degeneration and other human disease such as cancer or neurodegeneration.

4. Anticipated effects and future applications of research

Our further studies would provide us with important clues towards a new therapeutic approach against various human diseases, such as neurodegeneration, cancer and metabolic disorders.

Autophagy



Physiological roles of autophagy

1. Starvation-induced autophagy

Supply of amino acids for macromolecule synthesis and energy production

Essential for early development and neonates

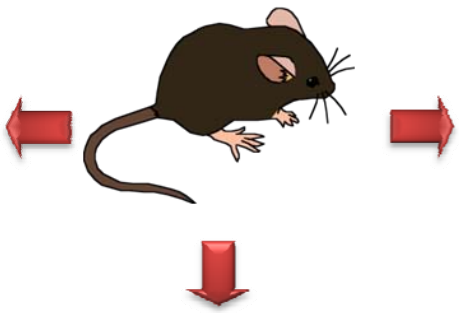
2. Constitutive autophagy

Global turnover of cellular proteins and organelles

Indispensable for cellular homeostasis

Autophagy fights various diseases

Conditional knockout mice for autophagy
(*Atg7* cKO mice)



Nervous system
Nestin Cre tg (Brain)
Pcp2 Cre tg (Purkinje cells)
POMC Cre tg (Hypothalamus)
SF-1 Cre tg (Ventromedial hypothalamus)
Vacht Cre tg (Motor neuron)
TH Cre tg (Dopaminergic neuron)

Metabolic pathway
Alb Cre tg (Liver)
Mx1 Cre tg (Liver)
RIP-Cre tg (beta-pancreatic cells)
MCK-Cre tg (Muscle)
Fabp4 Cre tg (Adipose tissue)
MLK Cre tg (Skeletal muscle)

Others
villin Cre tg (Intestinal epithelium)
Vav Cre tg (Hematopoietic cells)
CGA cre tg (Pituitary gland)

Neurodegeneration

Hepatitis

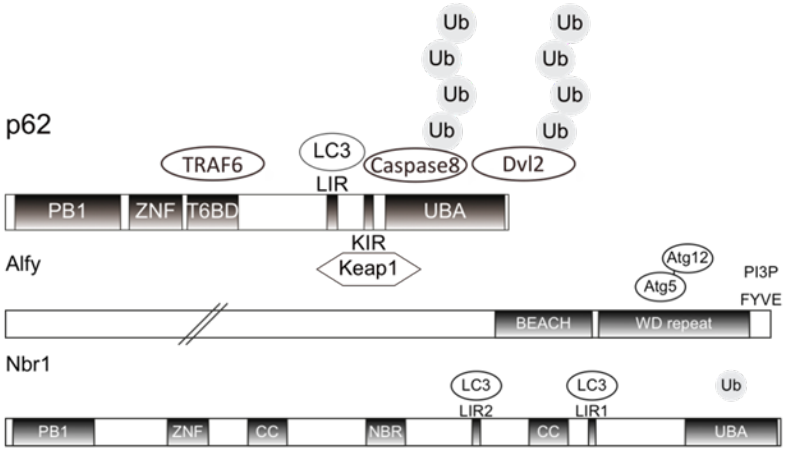
Anemia

Diabetes

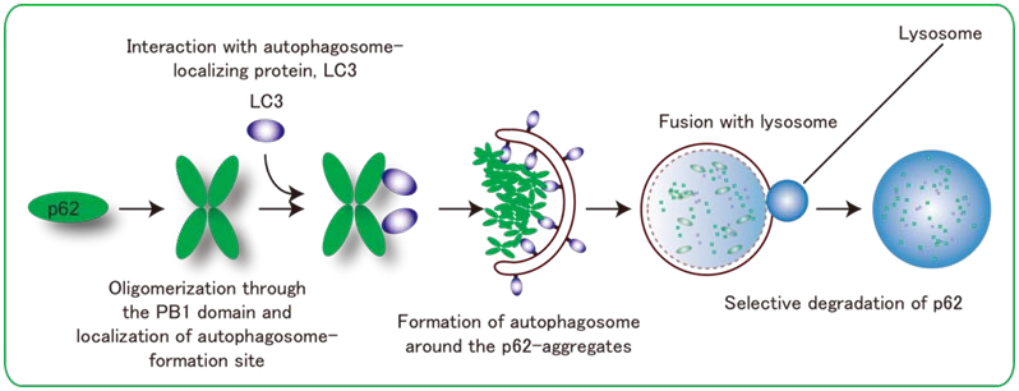
Colitis

Myopathy

Autophagy-selective substrates related to human diseases



Proposal model of p62 turnover through autophagy

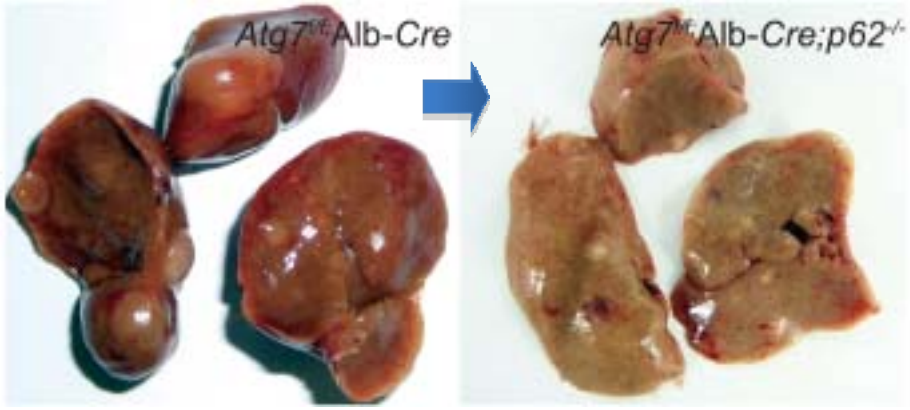


Involvement of p62-accumulation in tumor development

Suppression of tumor development

Atg7 KO

Atg7 p62 DKO



Takamura A., et al., *Genes Dev* 2011, Inami Y., et al., *J Cell Biol* 2011

Research framework

1. Molecular dissection of selective autophagy in mammals.
2. Generation and analysis of knockout mice related to selective autophagy.
3. Generation of the monitor mice for autophagy-specific substrates.

Future view

1. Elucidation of a shared pathogenesis in cancer, metabolic diseases and neurodegeneration.
2. *In vivo* monitoring of disease-related autophagy substrates under various conditions.
3. Valuable in development of a new therapeutic approach against various human diseases, such as neurodegeneration, cancer and metabolic disorders.