Drug discovery, Healthcare

Autophagy in lifestyle-related diseases

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Researchmap https://researchmap.jp/read0085516

Abstract

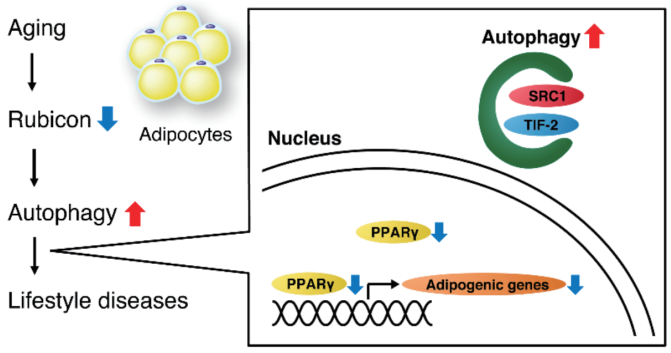
Autophagy is an intracellular bulk degradation system that plays a pivotal role in the maintenance of cellular homoeostasis. The systemic decline in autophagic activity with age impairs homeostasis in several tissues, leading to age-related diseases. We previously showed that a protein called Rubicon, which inhibits autophagy, is upregulated in aging tissues. Recently we found that, in contrast to other tissues, such as the liver and the kidneys, Rubicon levels were decreased in the adipose tissue of aged mice, resulting in increased autophagic activity.

Rubicon knockout in adipocytes causes fat atrophy and hepatic lipid accumulation due to reductions in the expression of adipogenic genes, which can be recovered by activation of PPARγ. SRC-1 and TIF2, coactivators of PPARγ, are degraded by autophagy in a manner that depends on their binding to GABARAP family proteins and are significantly downregulated in Rubicon-ablated or aged adipocytes.

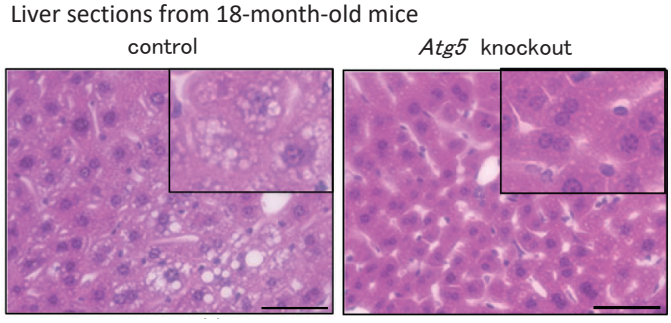
Significance of the research and Future perspective

We have revealed that Rubicon plays an essential role in proper maintenance of adipocyte function and systemic metabolic homoeostasis by preventing excess basal autophagy.

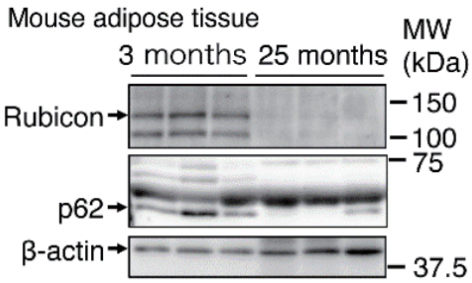
The absence of Rubicon in adipocytes occurs in aging and cause excess autophagy, resulting in lifestyle-related diseases due to impaired adipocyte functions. This study should promote the development of novel therapeutic strategies for lifestyle-related diseases by inhibiting autophagy on adipocytes.



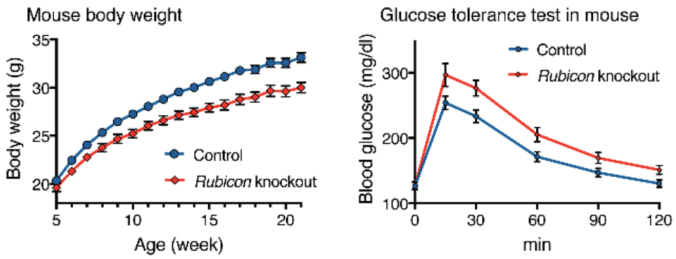
The proposed mechanism of adipose tissue aging.



Excess autophagy in adipocytes promotes age–related hepatic steatosis.



Rubicon levels in mouse adipose tissue decrease with age.



Deletion of Rubicon in adipose tissue leads to leanness and glucose intolerance.

Patent

Treatise Yamamuro, Tadashi; Kawabata, Tsuyoshi; Fukuhara, Atsunori et al. Age-dependent loss of adipose Rubicon promotes metabolic disorders via excess autophagy. Nat Commun. 2020; 11(1): 4150. doi: 10.1038/s41467-020-17985-w
Nakamura, Shuhei; Oba, MMasaki; Suzuki, Mari et al. Suppression of autophagic activity by Rubicon is a signature of aging. Nat Commun. 2019; 10(1): 847. doi: 10.1038/s41467-019-08729-6

URL https://yoshimori-lab.com/

Keyword autophagy, lifestyle-related diseases, aging, rubicon, drug discovery