Stagnation of autophagy as a driver of kidney disease progression in aging and obesity

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Abstract

Chronic kidney disease (CKD) affects nearly one in five people in Japan, making it a significant public health issue. Aging and obesity are closely linked to CKD development and progression. This study aimed to uncover mechanisms counteracting CKD progression. Our previous research showed that autophagy in kidney proximal tubular epithelial cells (PTECs) has protective effects against age- and obesity-related kidney disease. However, as the disease progresses, "autophagic stagnation" occurs, where lysosomal stress and dysfunction inhibit further autophagy activation. However, the compensatory mechanisms maintaining PTEC homeostasis under these conditions were unclear.

This study demonstrated that impaired autophagy in PTECs during aging or obesity induces fibroblast growth factor 21 (FGF21) production, which is known for its anti-aging and anti-obesity properties. FGF21 was found to alleviate autophagic stagnation and promote mitochondrial biogenesis, thereby reducing CKD progression during aging and obesity.

Background & Results

CKD has emerged as a major public health concern, with aging and obesity contributing significantly to its development and progression. Autophagy is an essential cellular process that preserves homeostasis by ensuring the quality control of cytoplasmic components and optimizing cellular energy states. Our recent studies have shown that autophagy in PTECs plays a key role in countering kidney disease during aging and obesity. Additionally, we discovered that aging and obesity induce "autophagic stagnation," a condition where lysosomal stress and dysfunction impede further activation of autophagy. The compensatory mechanisms that act against autophagic stagnation, however, remained unclear.

To explore this, we created autophagy-deficient mice by deleting the Atg5 gene in PTECs and studied them under aging and obesity models. Both models showed significant FGF21 production increases in autophagy-deficient mice. Additionally, PTEC-specific FGF21 knockout (KO) mice were studied under aging and obesity conditions. The results revealed a marked increase in vacuolar formation, identified as enlarged lysosomes, in the PTECs of FGF21 KO mice, along with a worsening of autophagic stagnation.

Further comparison between autophagy-deficient and double KO (autophagy-deficient plus FGF21-deficient) mice revealed that double KO mice experienced more severe CKD progression and exhibited reduced mitochondrial biogenesis and abnormalities. These findings suggest FGF21, produced in response to autophagy deficiency, plays a protective role by mitigating autophagic stagnation and supporting mitochondrial biogenesis.

Significance of the research and Future perspective

This study opens new avenues for CKD treatment strategies targeting FGF21 and autophagic stagnation. Eight years have passed since Dr. Yoshinori Ohsumi was awarded the Nobel Prize in Physiology or Medicine for his pioneering work on autophagy in 2016. We are hopeful that continued advancements in autophagy research will soon lead to therapeutic applications for kidney diseases, ultimately preventing kidney failure and the need for dialysis.

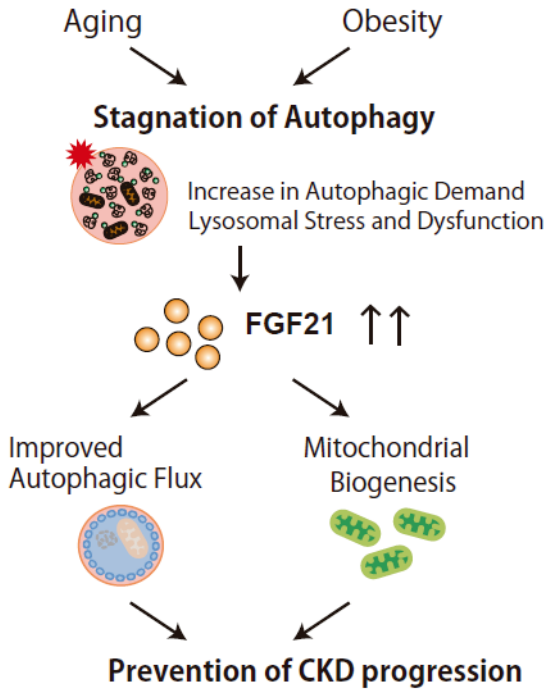

Figure 1

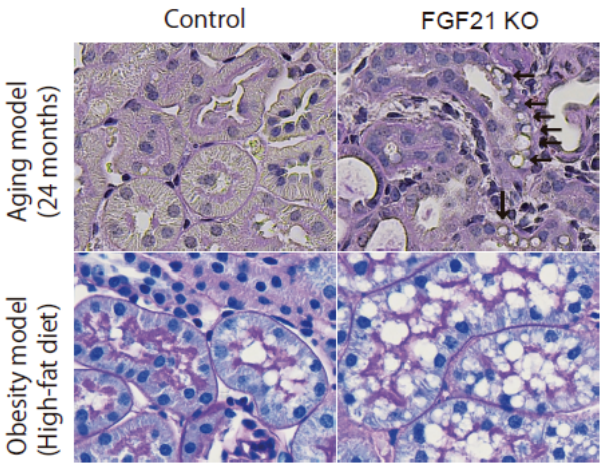

Figure 2

Patent	PCT/JP2022/024923
Treatise	Minami, Satoshi; Yamamoto, Takeshi; Isaka, Yoshitaka et al. FGF21 and autophagy coordinately counteract kidney disease progression during aging and obesity. Autophagy. 2024, 20(3), 489-504. doi: 10.1080/15548627.2023.2259282 Yamamoto, Takeshi; Isaka, Yoshitaka. Pathological mechanisms of kidney disease in ageing. Nat Rev Nephrol. 2024, 20(9), 603-615. doi: 10.1038/s41581-024-00868-4
URL	https://www.med.osaka-u.ac.jp/eng/introduction/research-5/internal/nephrology
Keyword	chronic kidney disease (CKD), aging, obesity, FGF21, autophagy