

30th Spring Congress of Korean Diabetes Association
in conjunction with 3rd Korea-Japan Diabetes Forum
May 12, 2017 BEXCO, Busan, Korea

Autophagy protects against kidney injury
related to aging, obesity and diabetes

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Pathogenesis of diabetic nephropathy

Hyperglycemia

- Activation of DAG-PKC pathway
- Accumulation of AGE
- Activation of polyol pathway
- Activation of hexosamine pathway
- ROS production

Strict glycemic control

Lipid abnormality

- High LDL-Cholesterol
- High FFAs

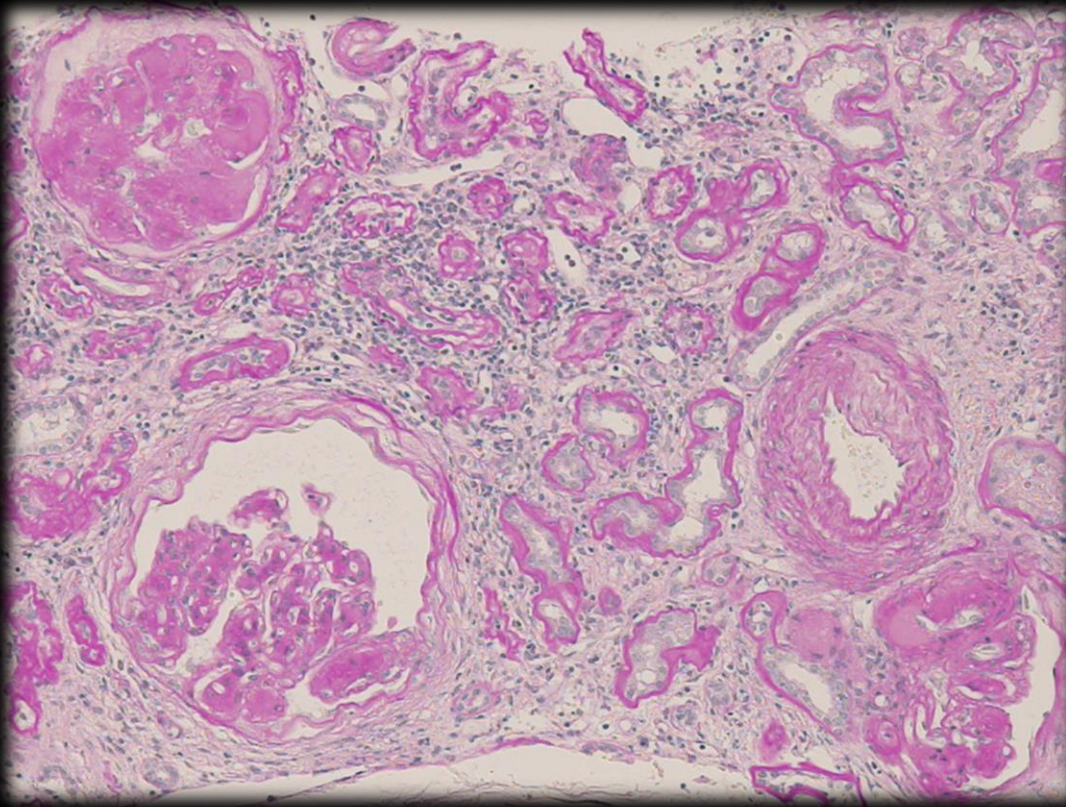
Lipid lowering
(Statin, Fibrate)

Hemodynamic changes

- Renin angiotensin system (RAS)

BP control
(RAS inhibitors)

Stage progression of diabetic nephropathy



Normoalbuminuria



Microalbuminuria



Overt proteinuria



Tubular cell damage



Renal dysfunction

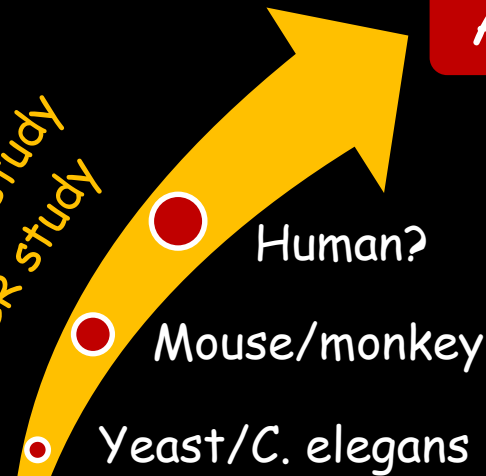


ESRD

Caloric restriction

- Life Span Elongation
- Anti-Oncogenic Effect
- Anti-Atherosclerogenic Effect
- Anti-Diabetic Effect
- Stress-Resistance
- **Renoprotective effect**

Aging study
CR study



Autophagy

Self-eating

Caloric restriction delays disease onset and mortality in Rhesus monkeys

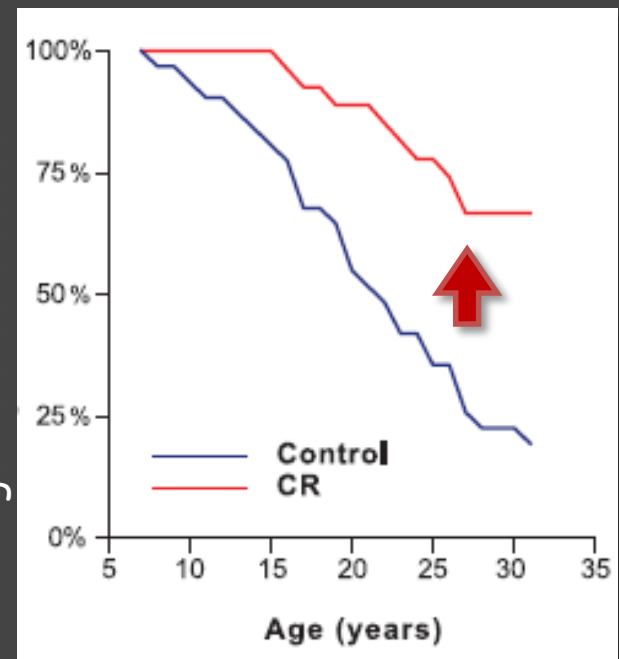
Ricki J. Colman., *Science* 10 July 2009 325: 201-204

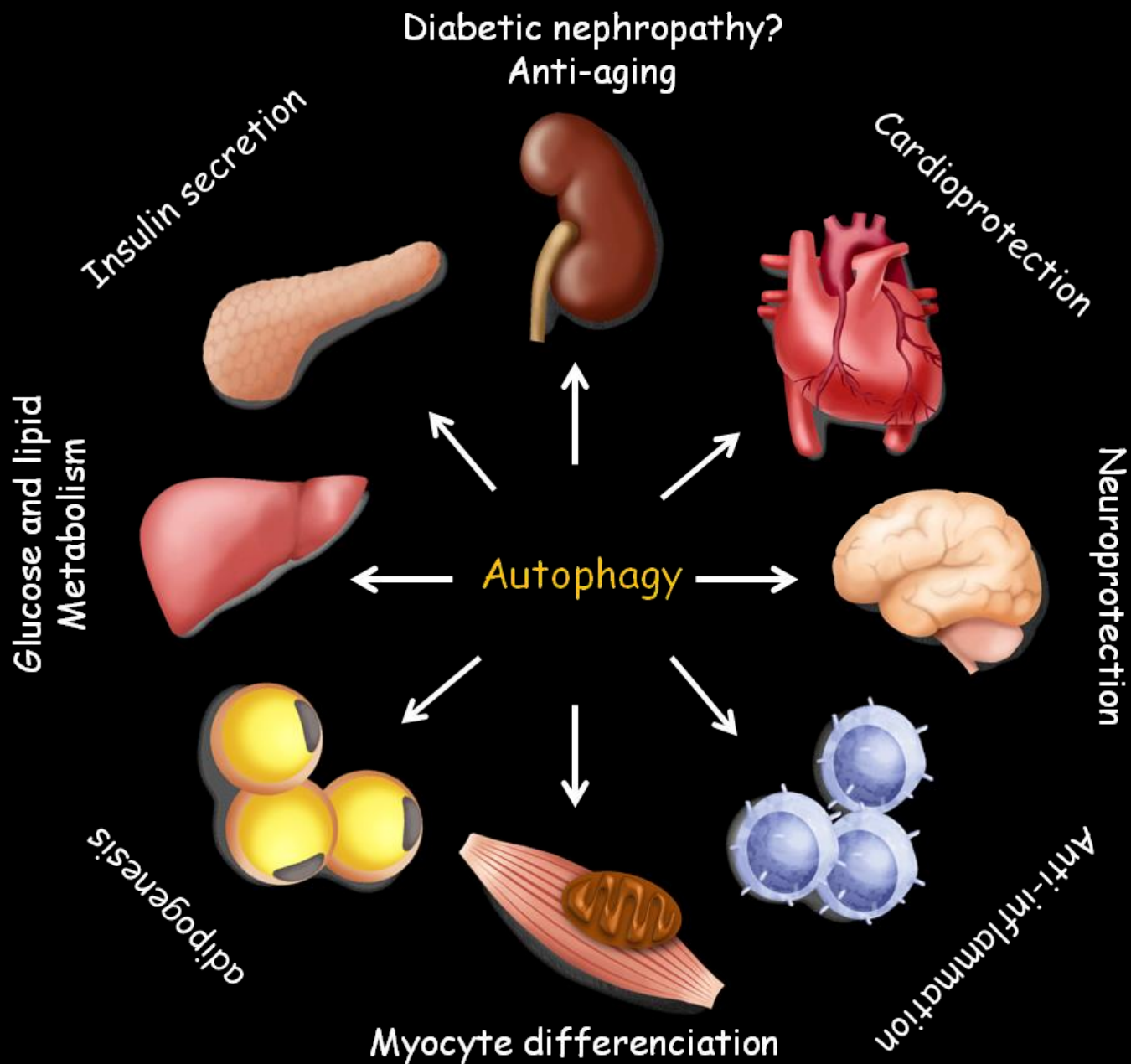
Ad-libitum fed

CR: 30%DR for 20ys

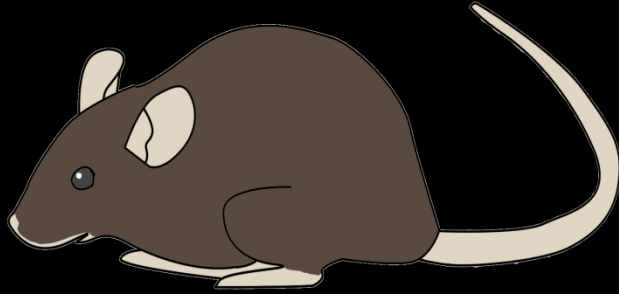


Percentage of animals without
Age-related disease



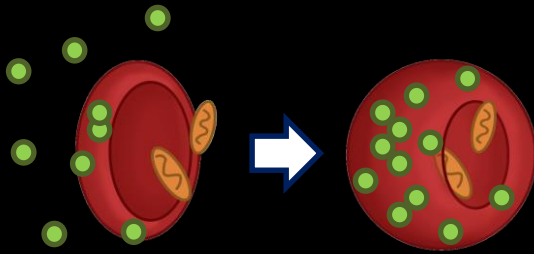


GFP-LC3 transgenic mouse

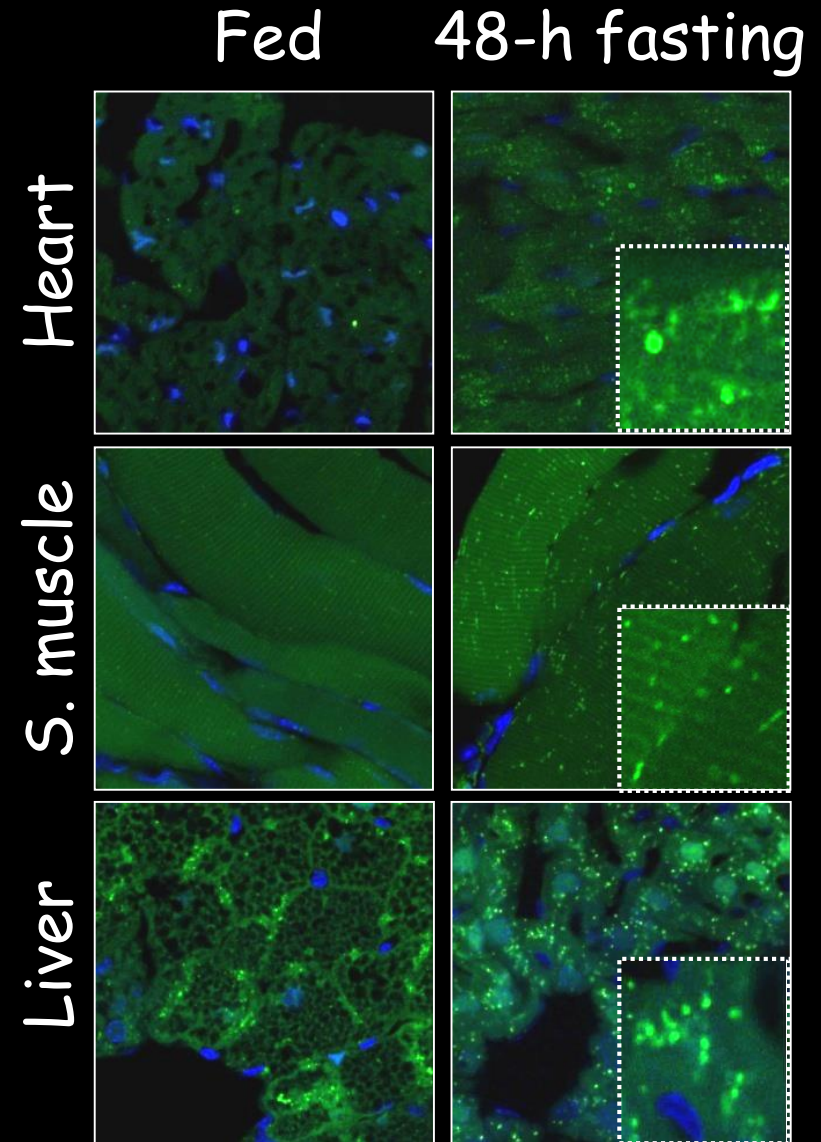


Inactive

Active



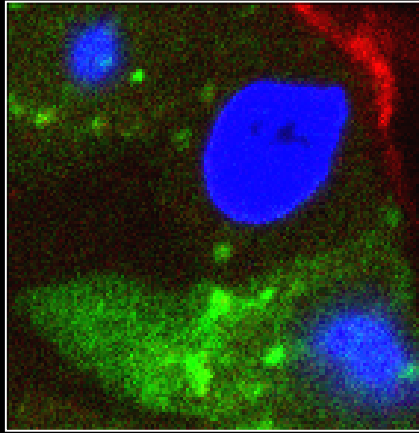
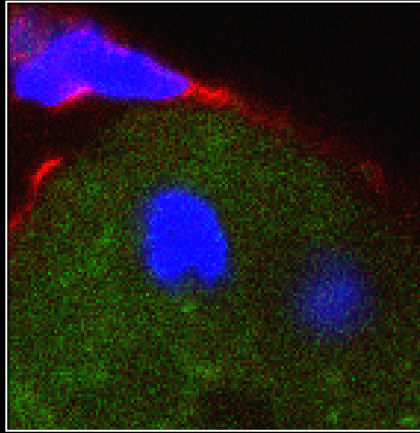
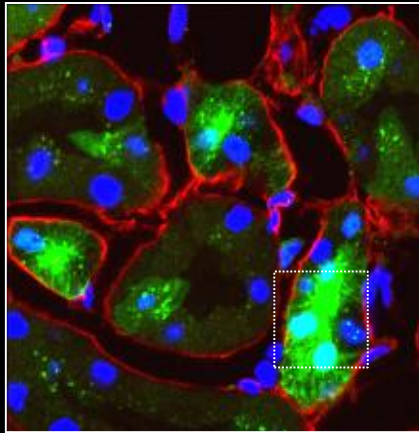
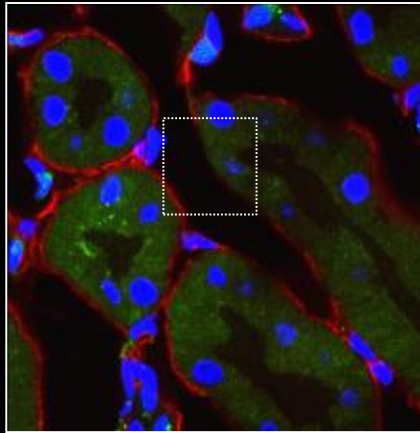
During autophagy activation,
LC3 localizes in the autophagosomal
membrane.



Autophagy in podocytes and proximal tubular cells

Ad-libitum

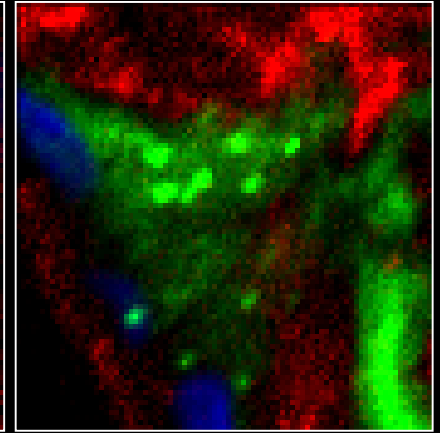
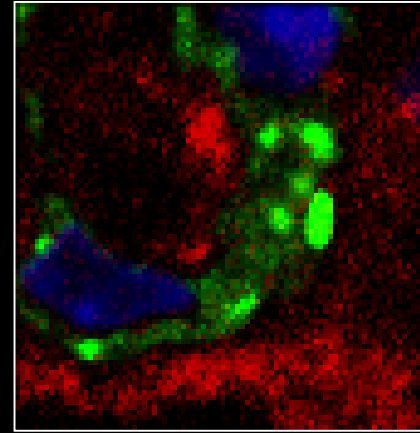
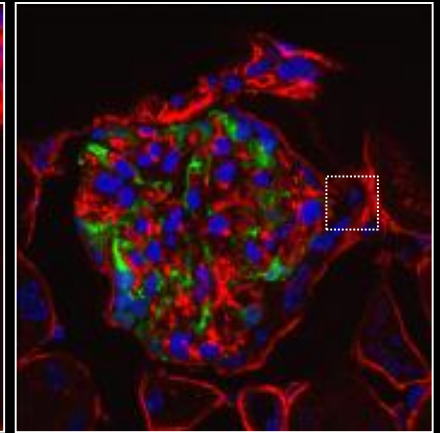
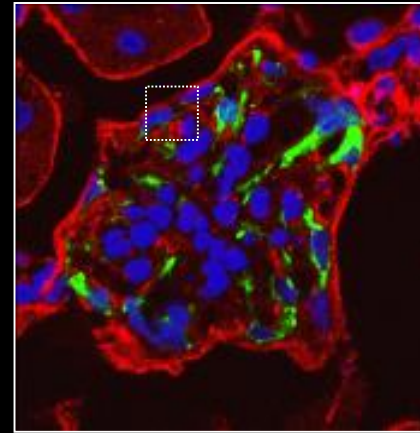
48h fast



Proximal tubular cells

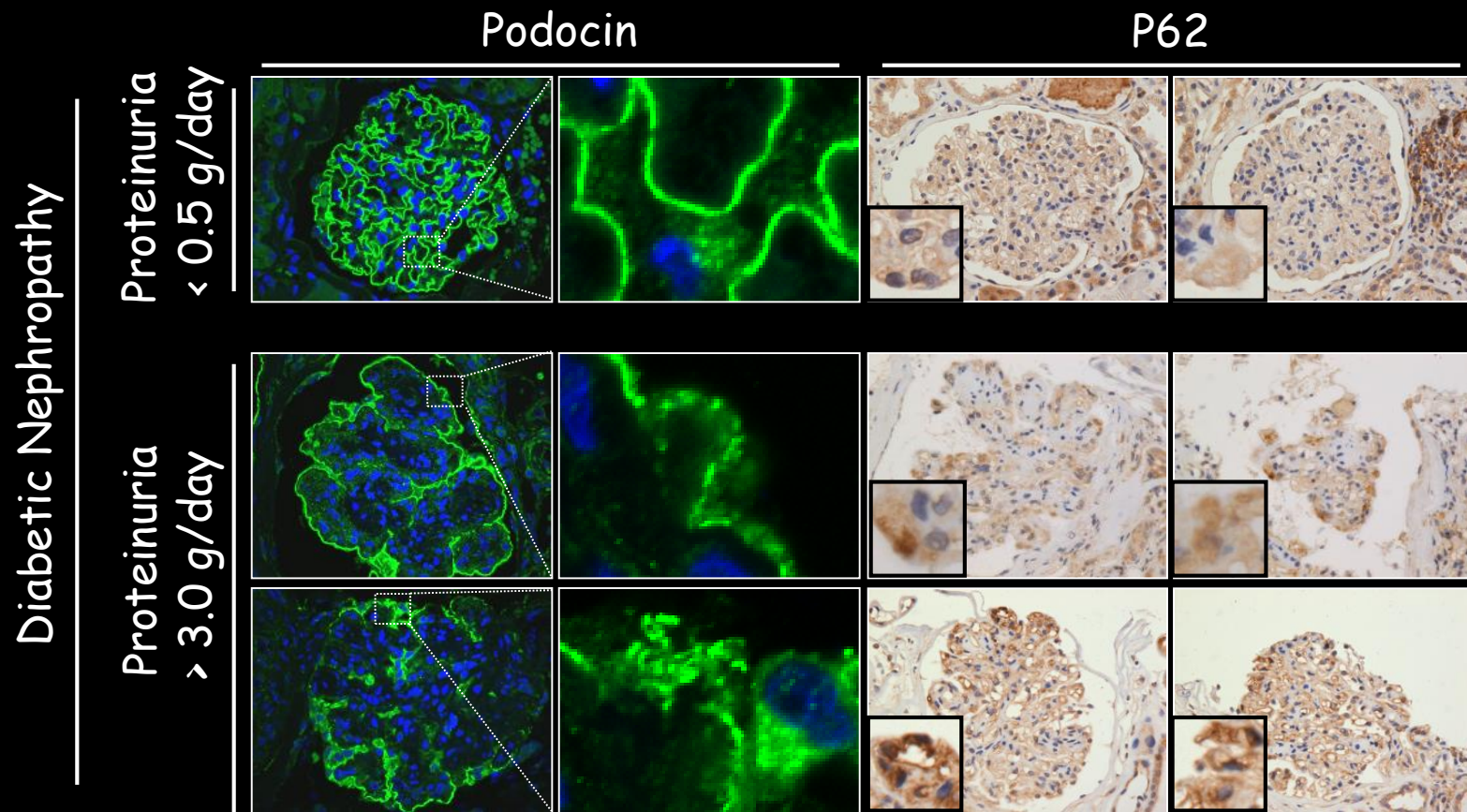
Ad-libitum

48h fast



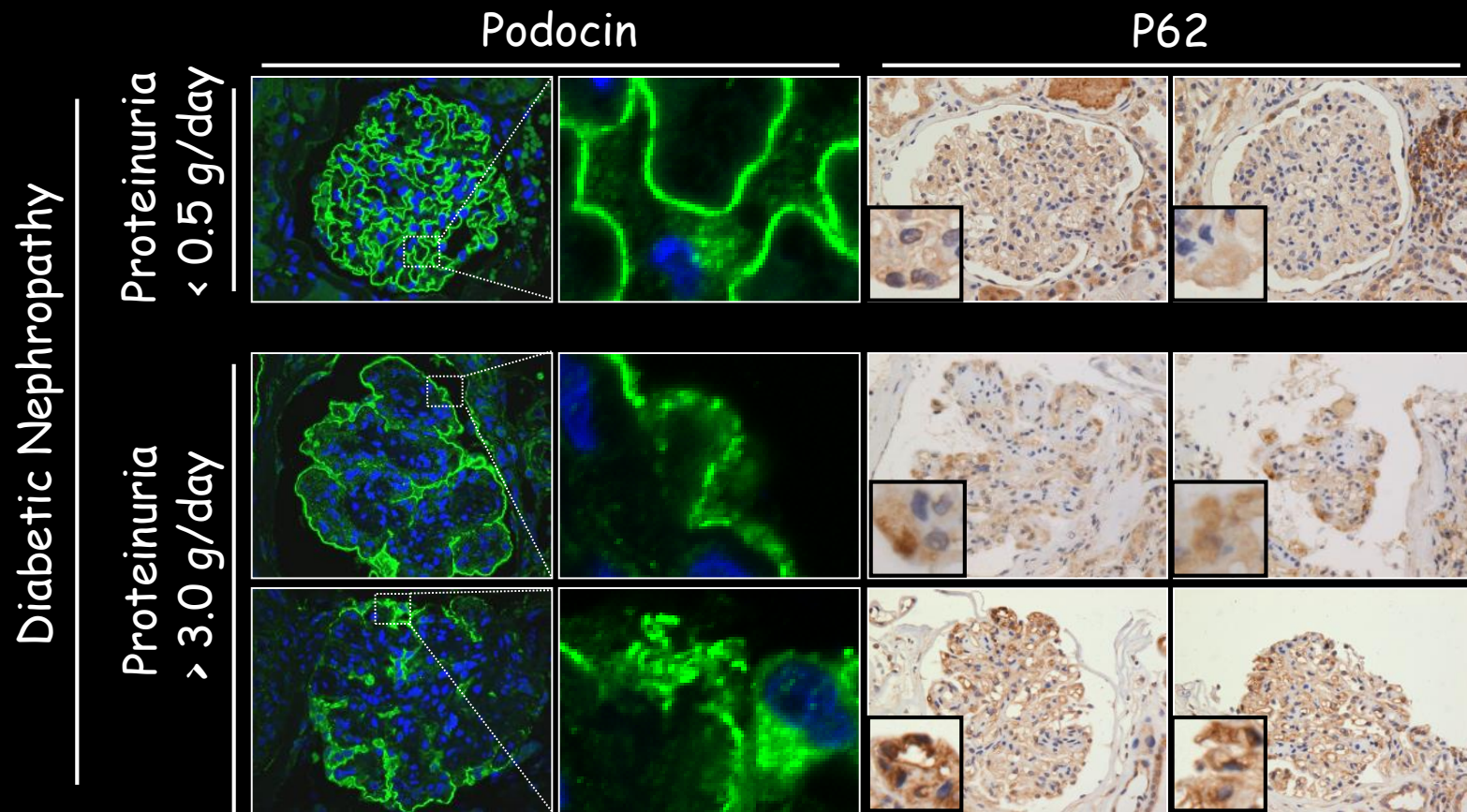
Glomerular epithelial cells
(Podocytes)

Autophagy is suppressed in podocytes of diabetic patients with massive proteinuria

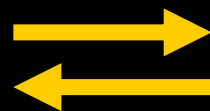


The accumulation of P62 protein is a marker of autophagy insufficiency.

Autophagy is suppressed in podocytes of diabetic patients with massive proteinuria



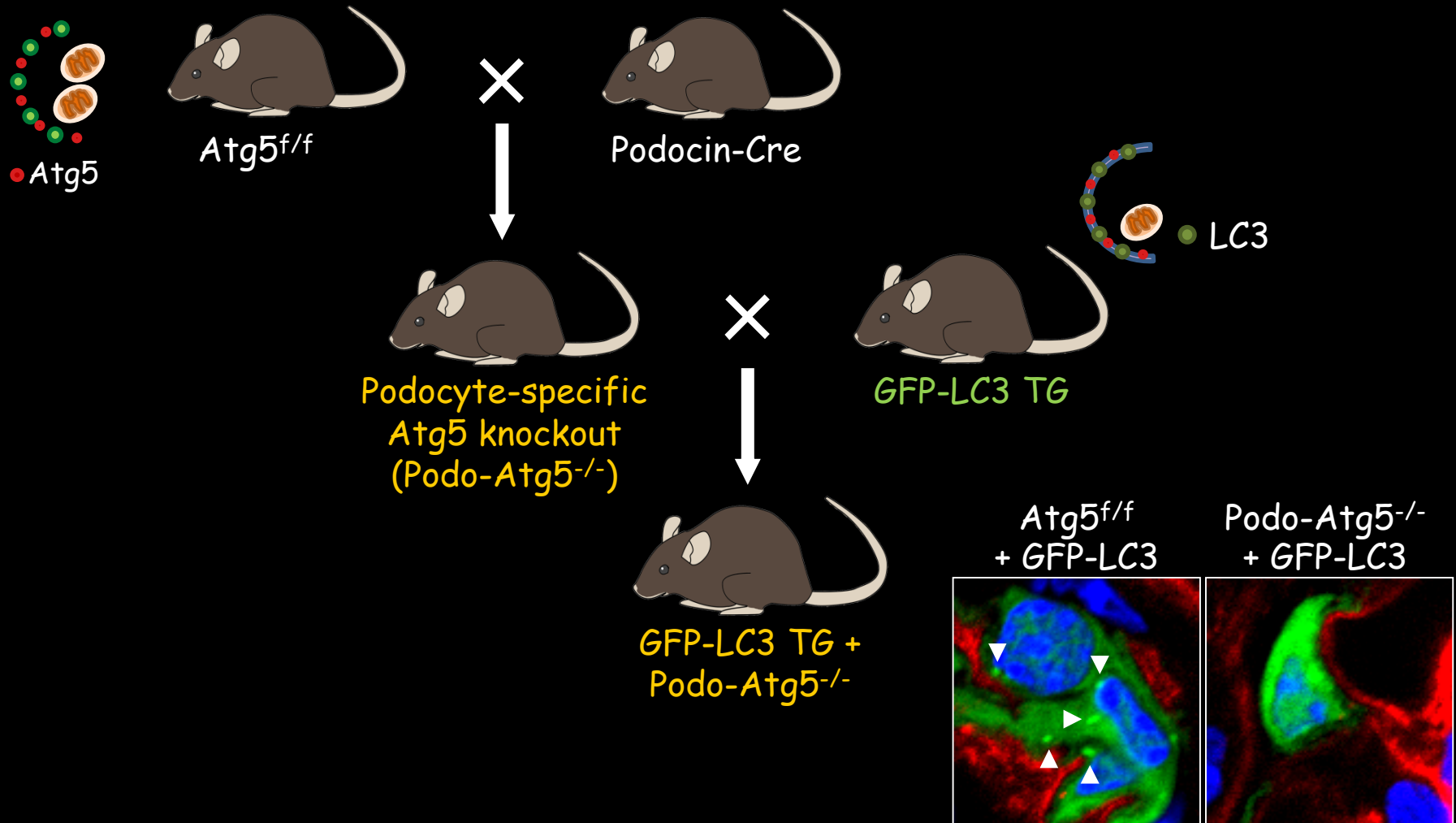
Podocyte damage
Massive proteinuria



Autophagy insufficiency

Causal relation ??

Podocyte-specific autophagy-deficient mice



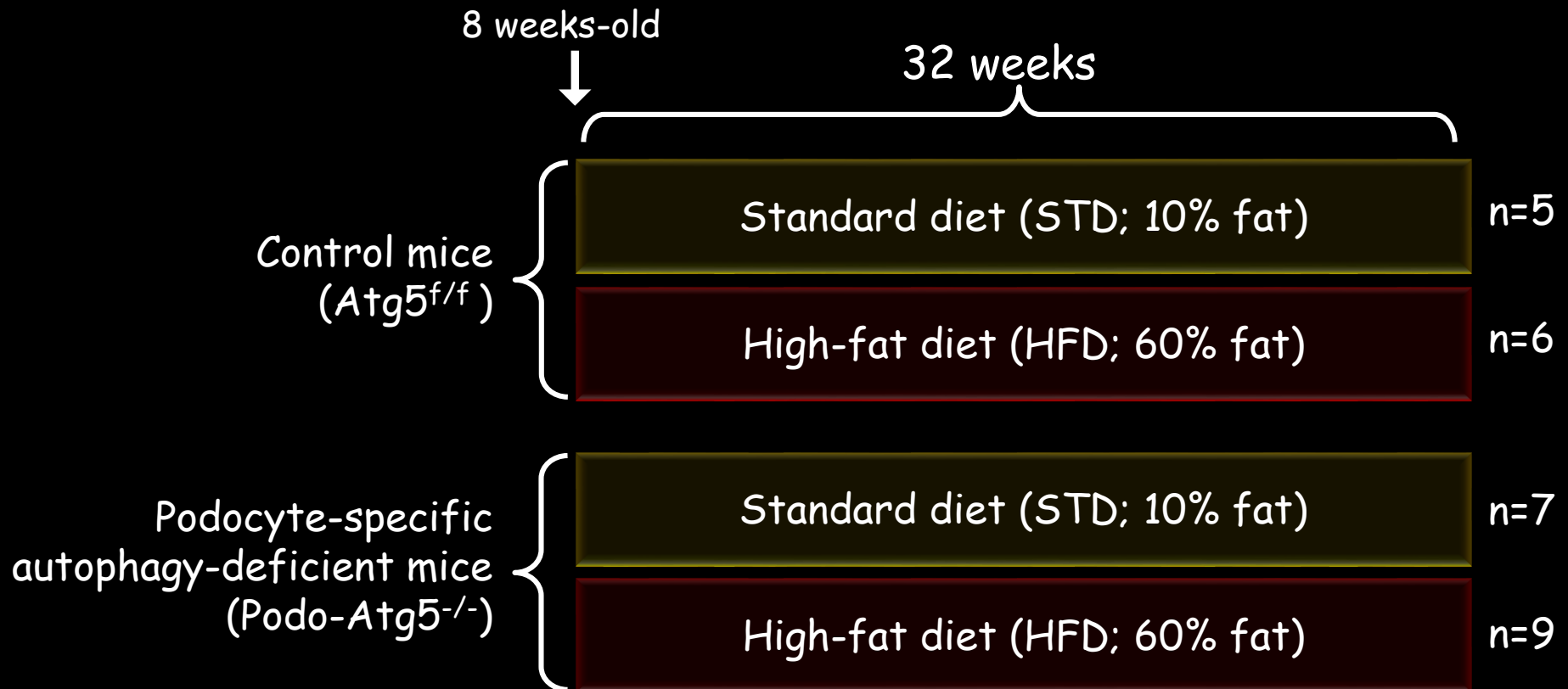
Dietary intervention study protocol

High-fat diet-induced obese type 2 model:

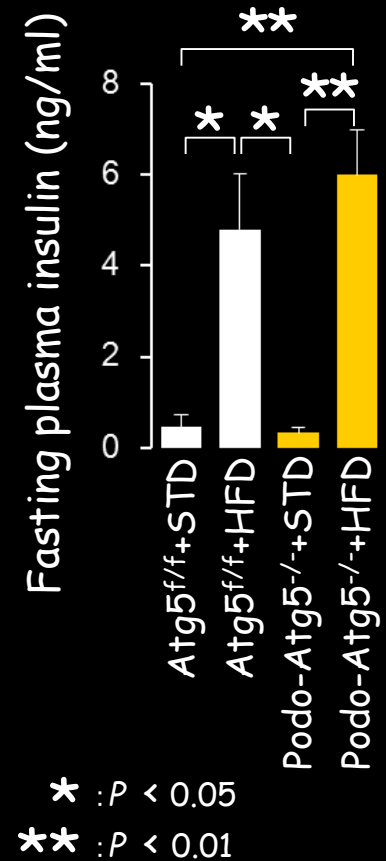
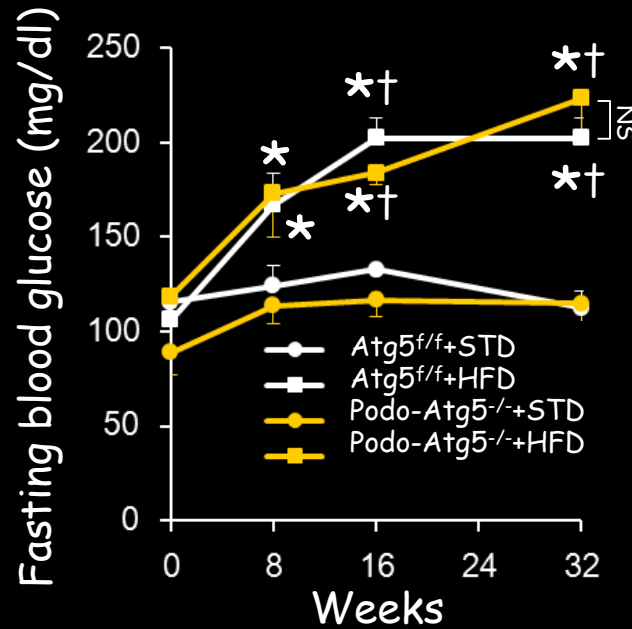
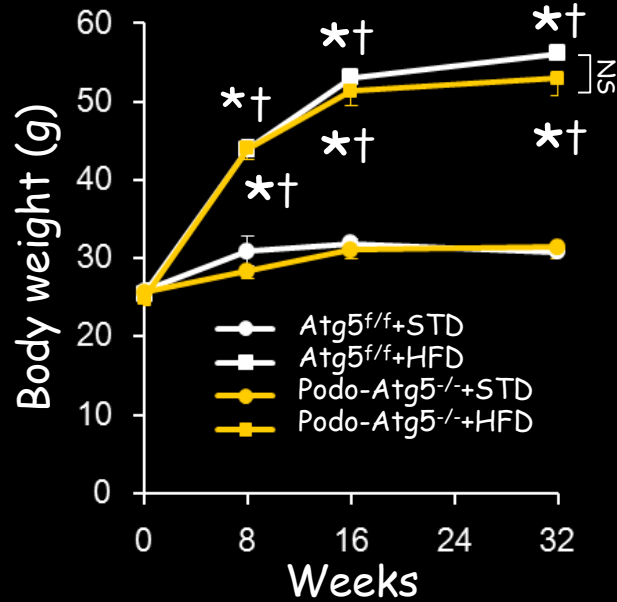
A mouse model to induce mild glomerular lesion and low grade albuminuria

Deji N. et al. AJP Renal Physiology (2009)

Kume S. et al. JASN (2007)



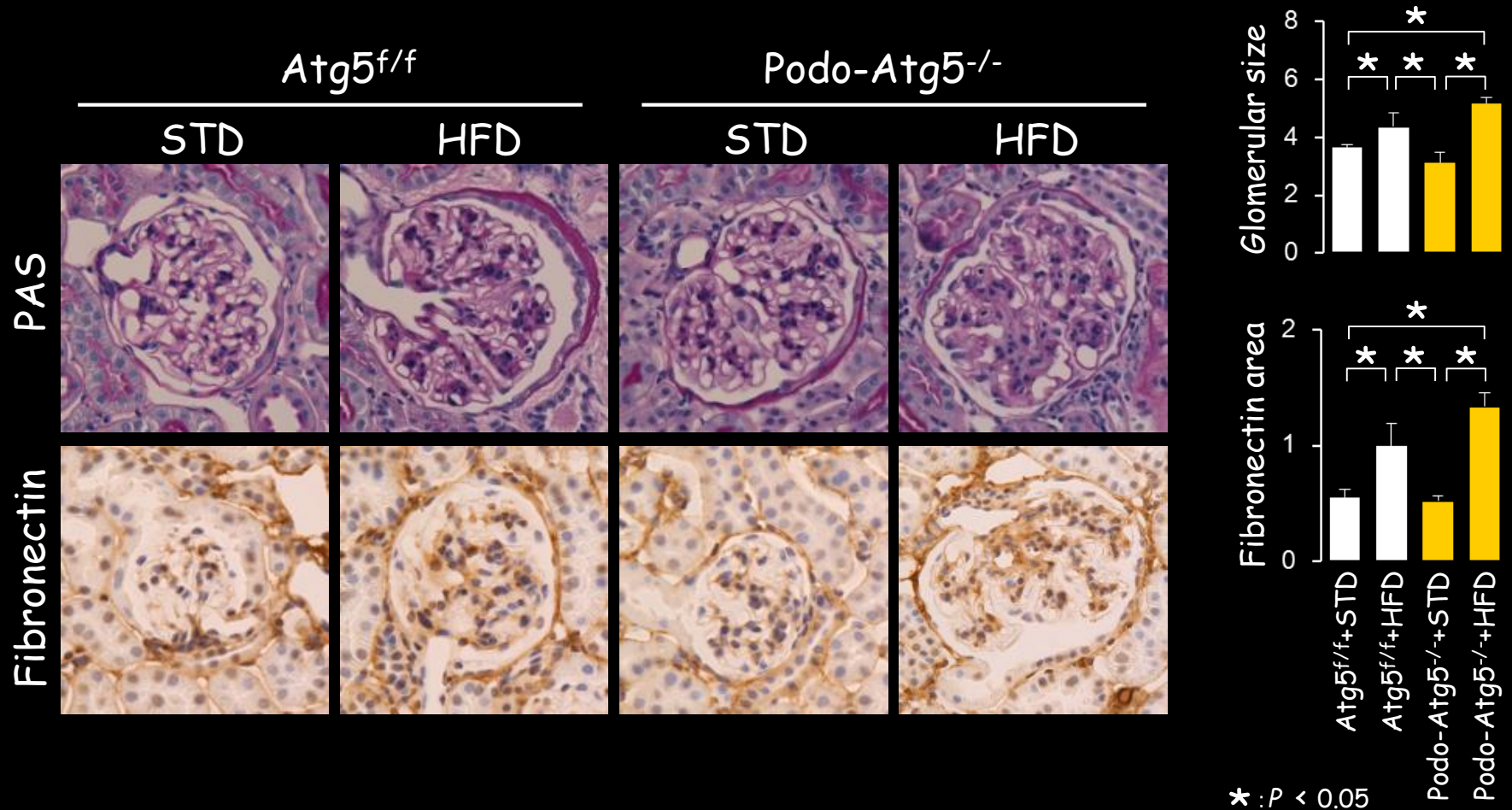
Podocyte-specific autophagy deficiency did not affect HFD-induced alteration of systemic glucose metabolism.



* : $P < 0.05$ vs. Atg5^{f/f}+STD
 † : $P < 0.05$ vs. Podo-Atg5^{-/-}+STD

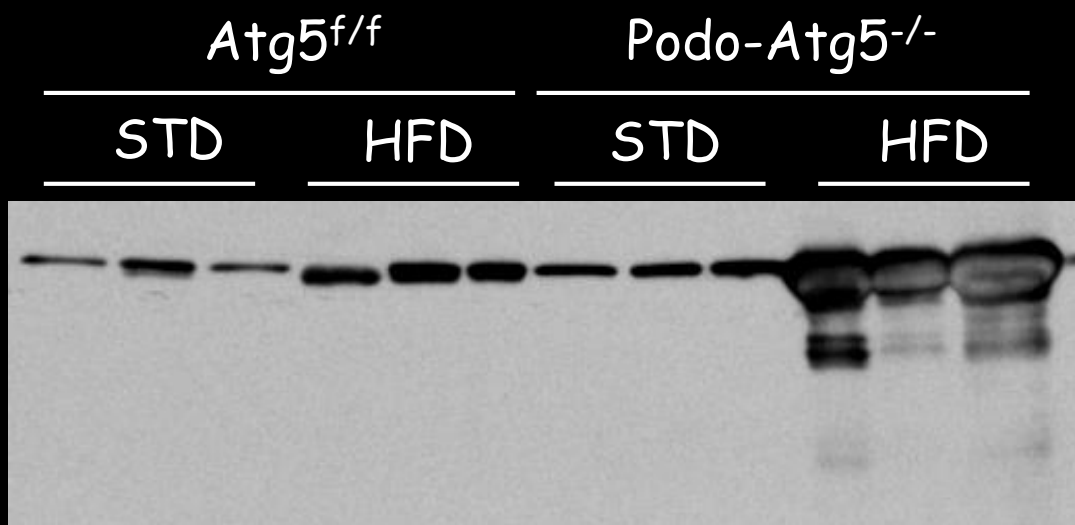
* : $P < 0.05$
 ** : $P < 0.01$

Podocyte-specific autophagy deficiency had no effect on HFD-induced glomerular hypertrophy and fibrosis.

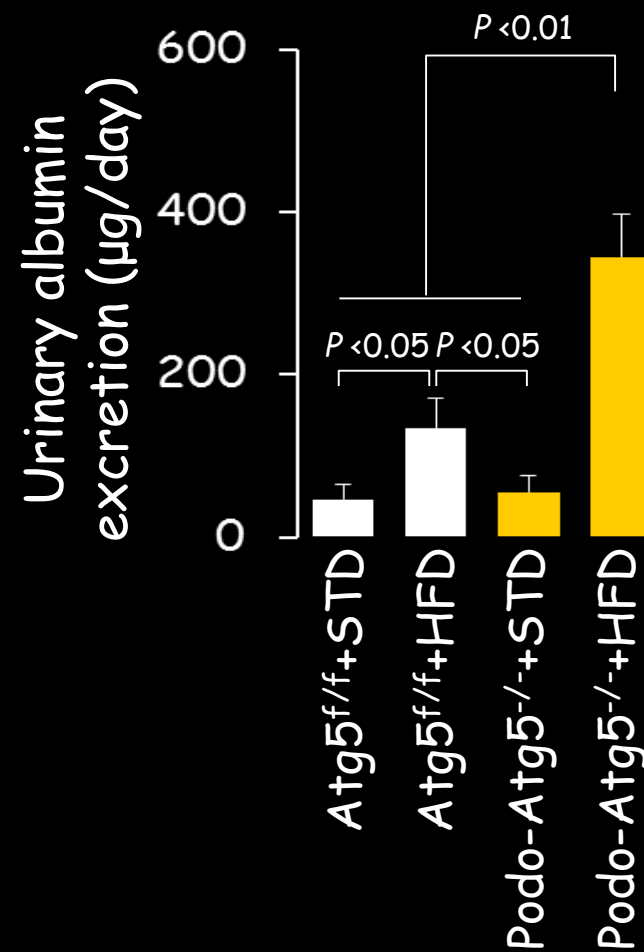


Podocyte-specific autophagy deficiency exacerbated HFD-induced increases in urinary albumin excretion.

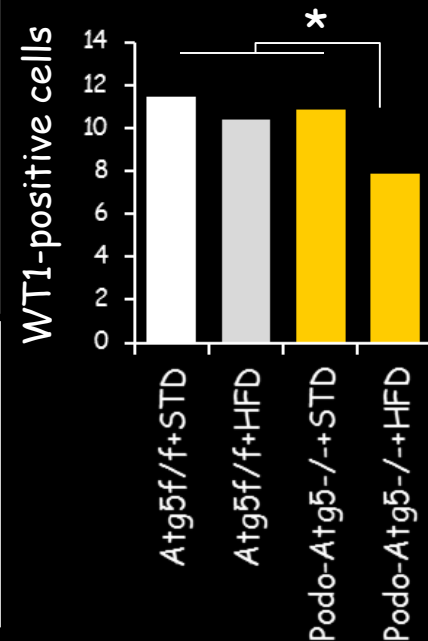
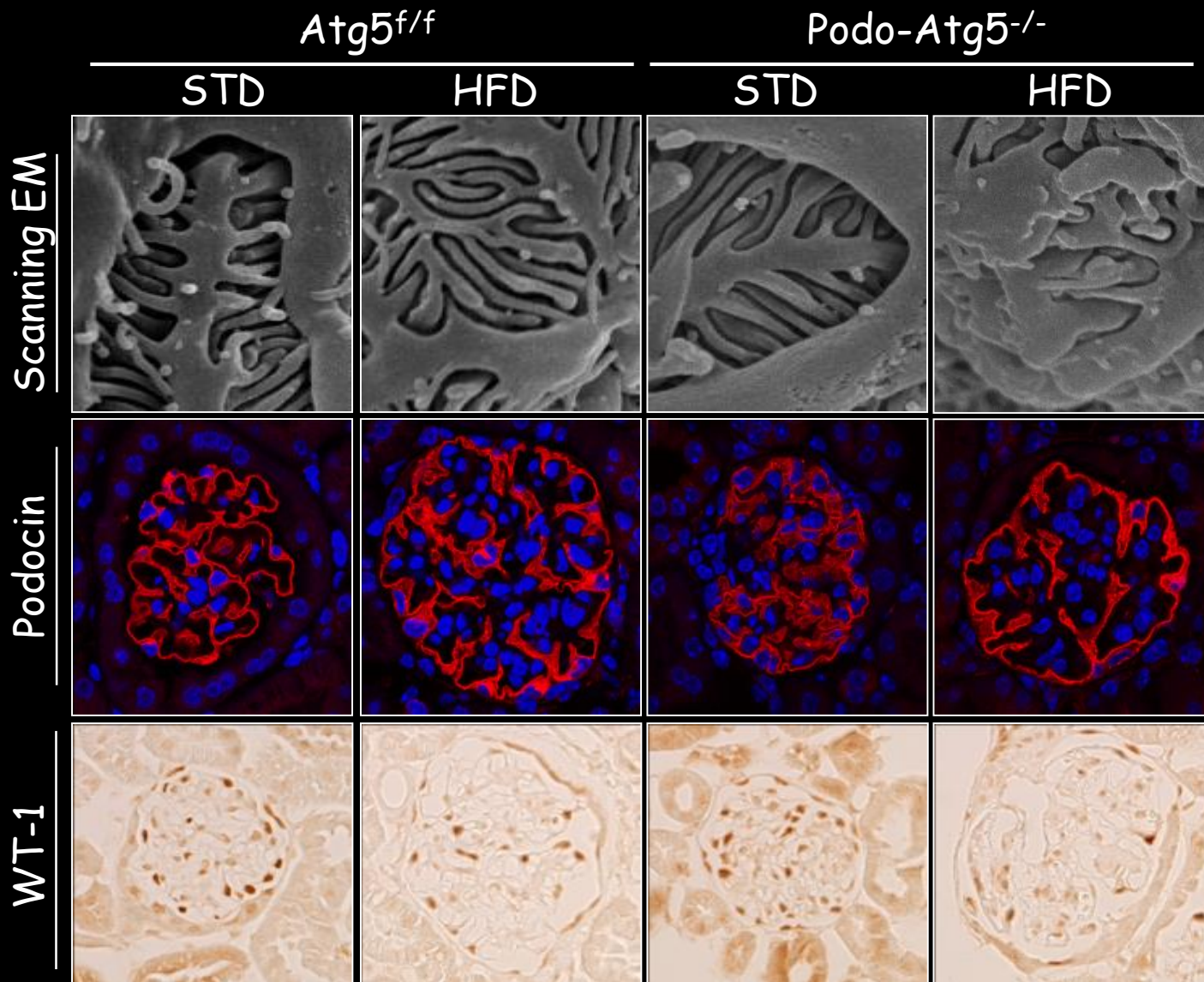
<Western blotting: anti-albumin antibody>



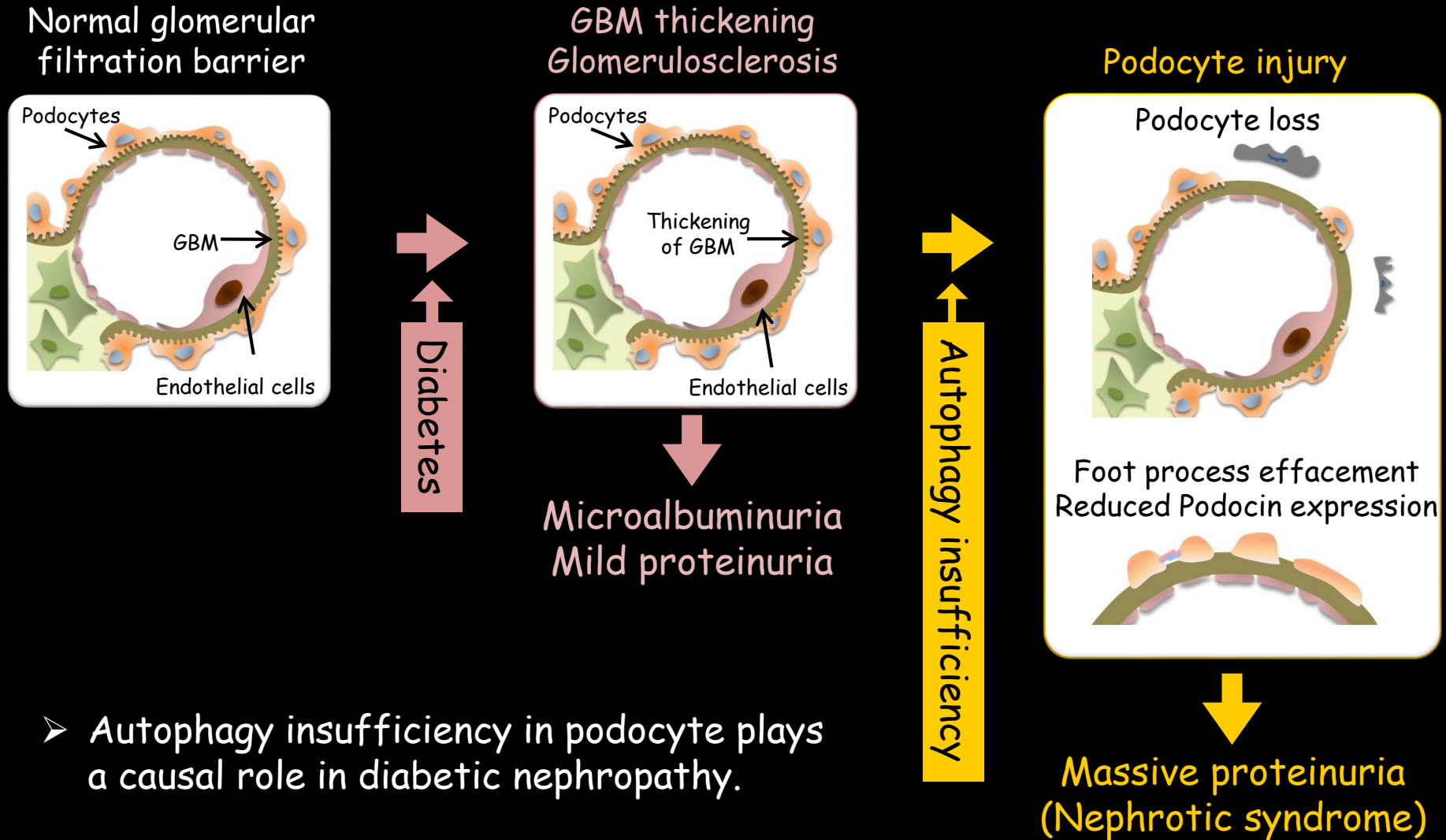
<ELISA>



Podocyte-specific autophagy deficiency caused podocyte dysfunction and podocyte loss only under diabetic condition.

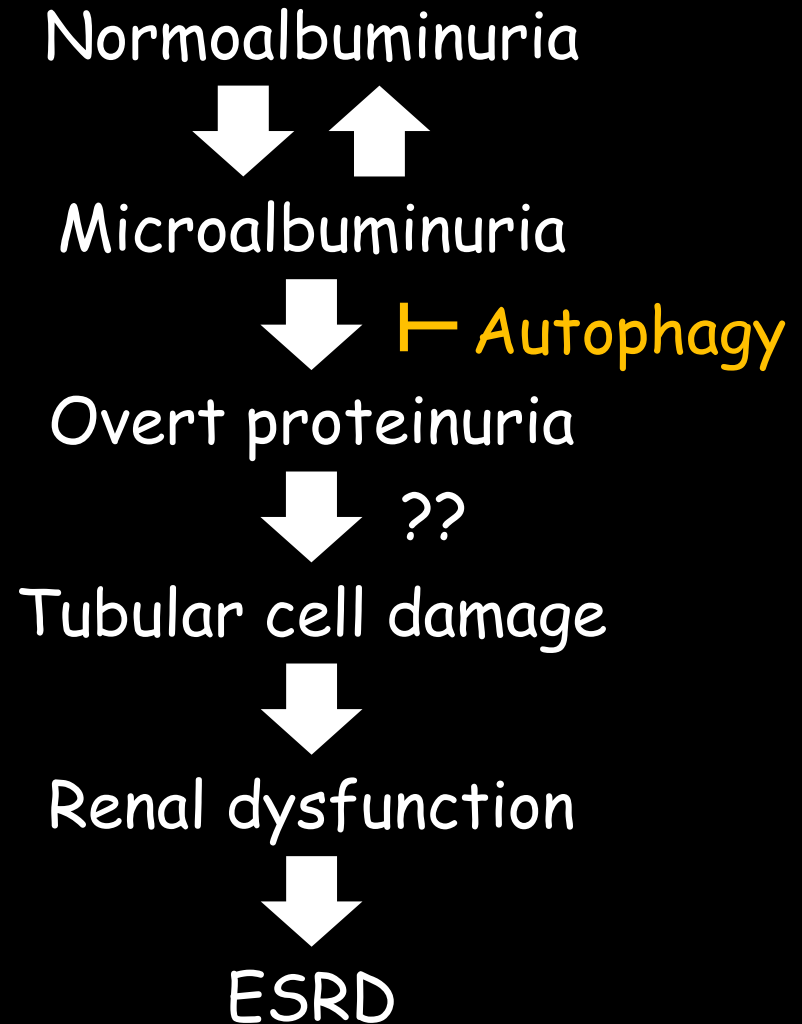
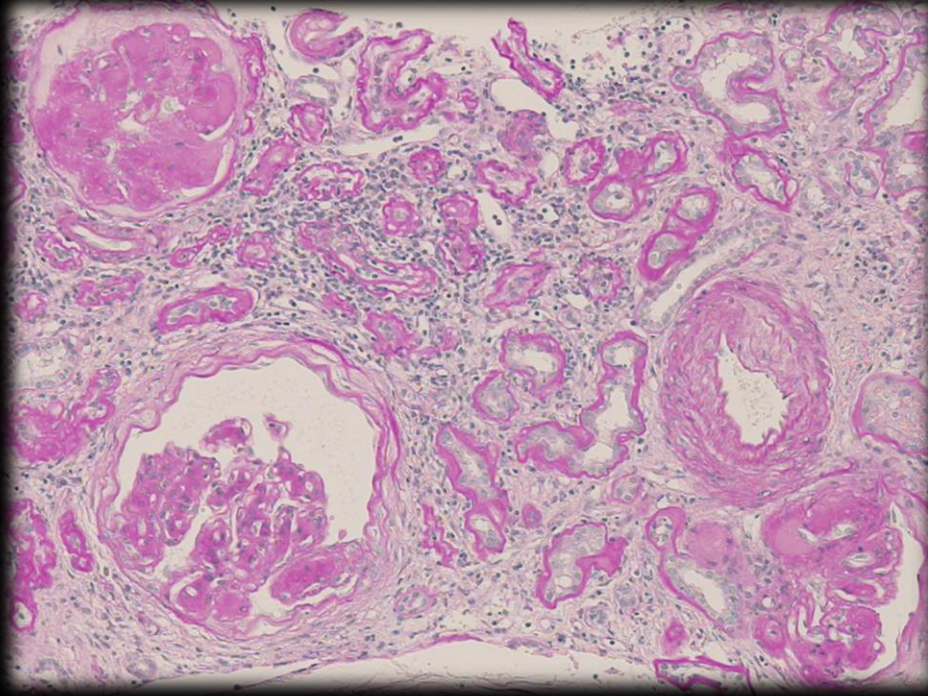


Summary of podocyte study

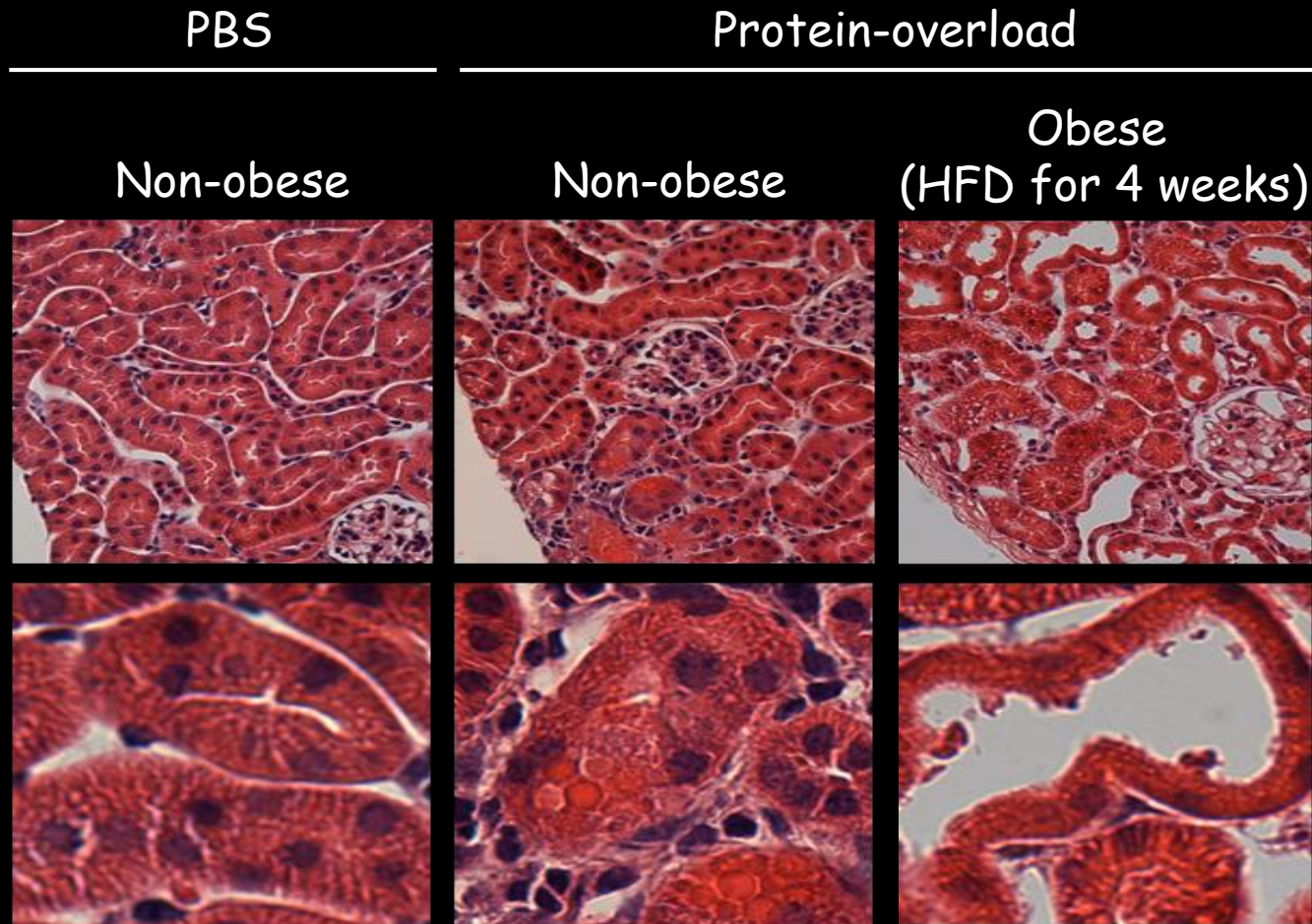


- Autophagy insufficiency in podocyte plays a causal role in diabetic nephropathy.
- These findings were consistent with the results of human biopsy study.

Therapeutic roles of autophagy in diabetic nephropathy



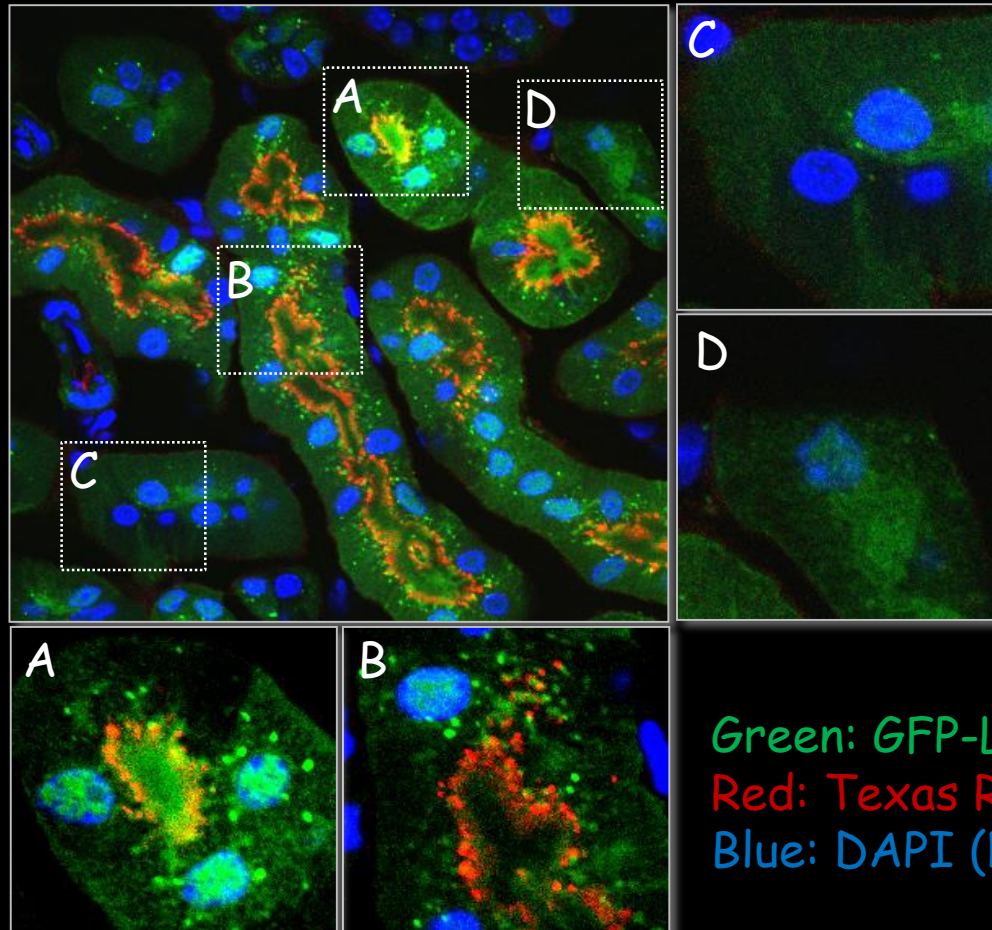
Proximal tubular cells in obese mice are more susceptible to proteinuria-related toxicity.



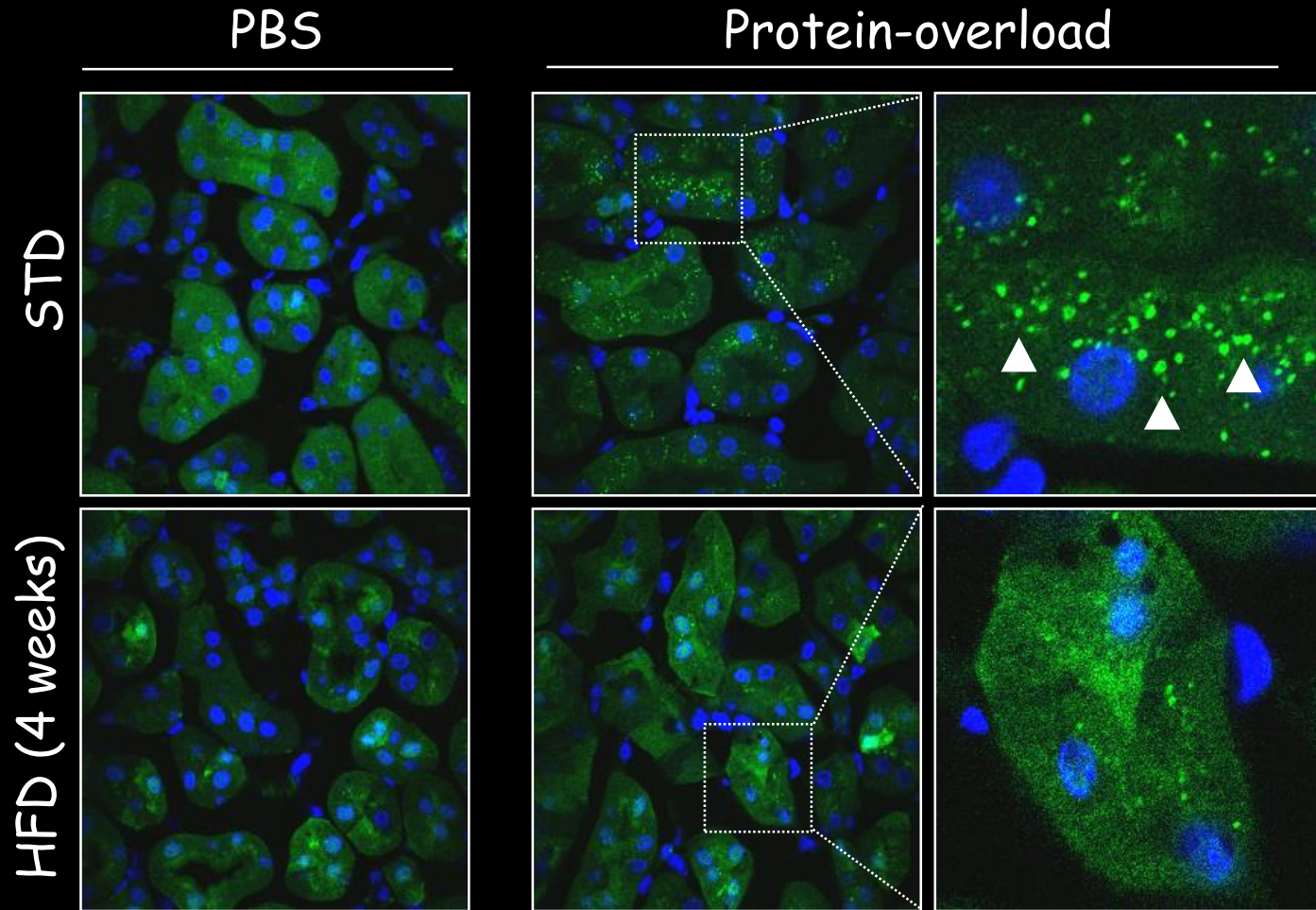
- Is autophagy involved in the molecular mechanism underlying obesity-mediated exacerbation of proteinuria-induced tubular cell damage?

Proteinuria induces autophagy in proximal tubular cells

Protein-overload model



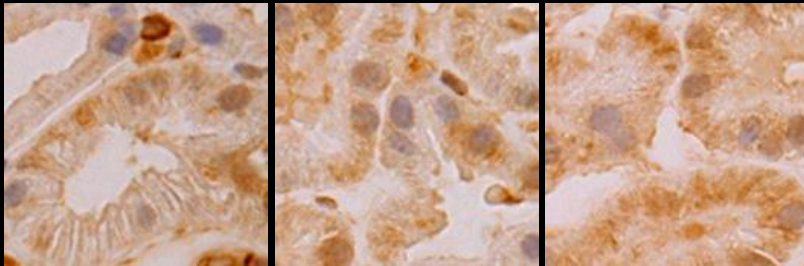
Obesity suppressed proteinuria-induced autophagy in proximal tubular cells



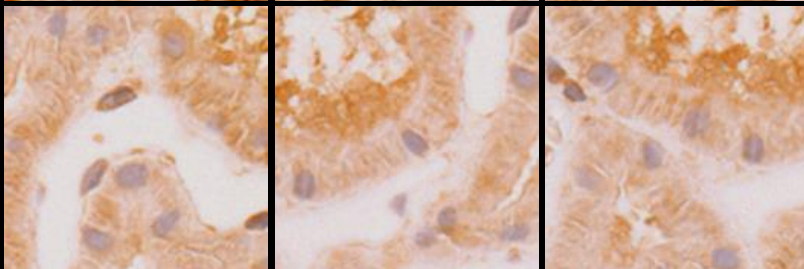
Autophagy is suppressed in proximal tubular cells of diabetic patients

Non-obese IgA nephropathy
with proteinuria (>1.0g/day)

Case 1

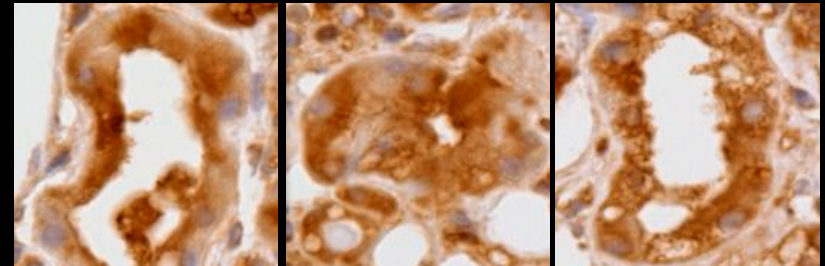


Case 2

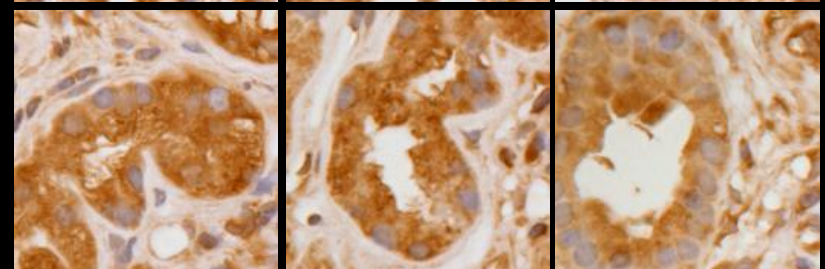


Obese diabetic nephropathy
with proteinuria (>1.0g/day)

Case 1

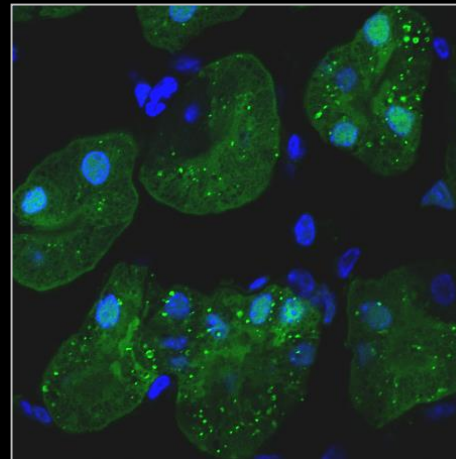
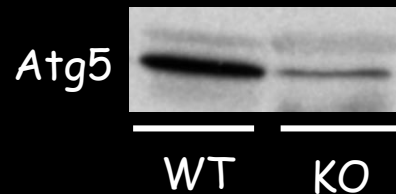


Case 2

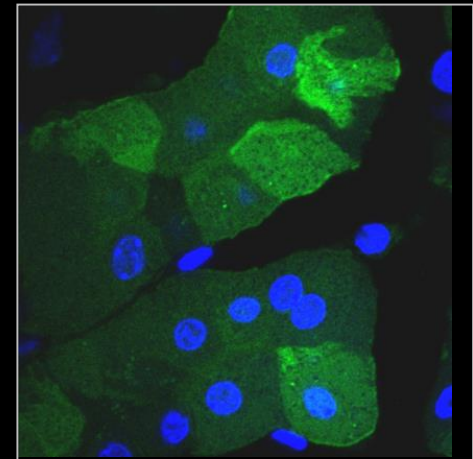


The accumulation of P62 protein is a marker of autophagy insufficiency.

Proximal tubular cell-specific autophagy-deficient mice

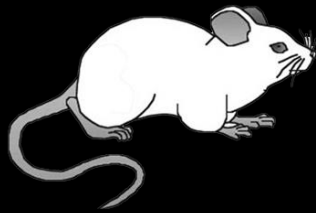


GFP-LC3TG
+ *Atg5^{f/f}*
+ Protein-overload



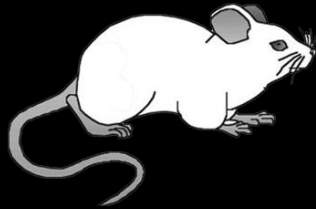
GFP-LC3TG
+ **PTEC-*Atg5*KO**
+ Protein-overload

Role of autophagy in proteinuria-induced tubular cell damage



Control (PBS) 11 days

Atg5-flox



Protein-overload (0.3g/kg/day) 11 days

Atg5-flox



Control (PBS) 11 days

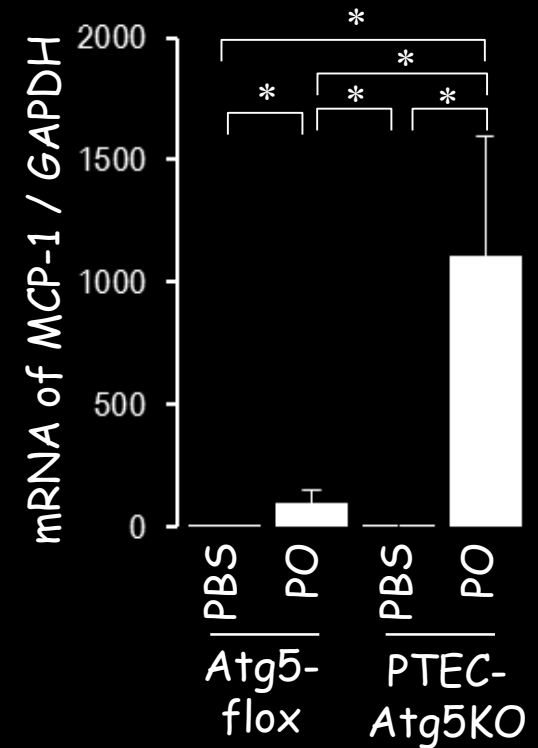
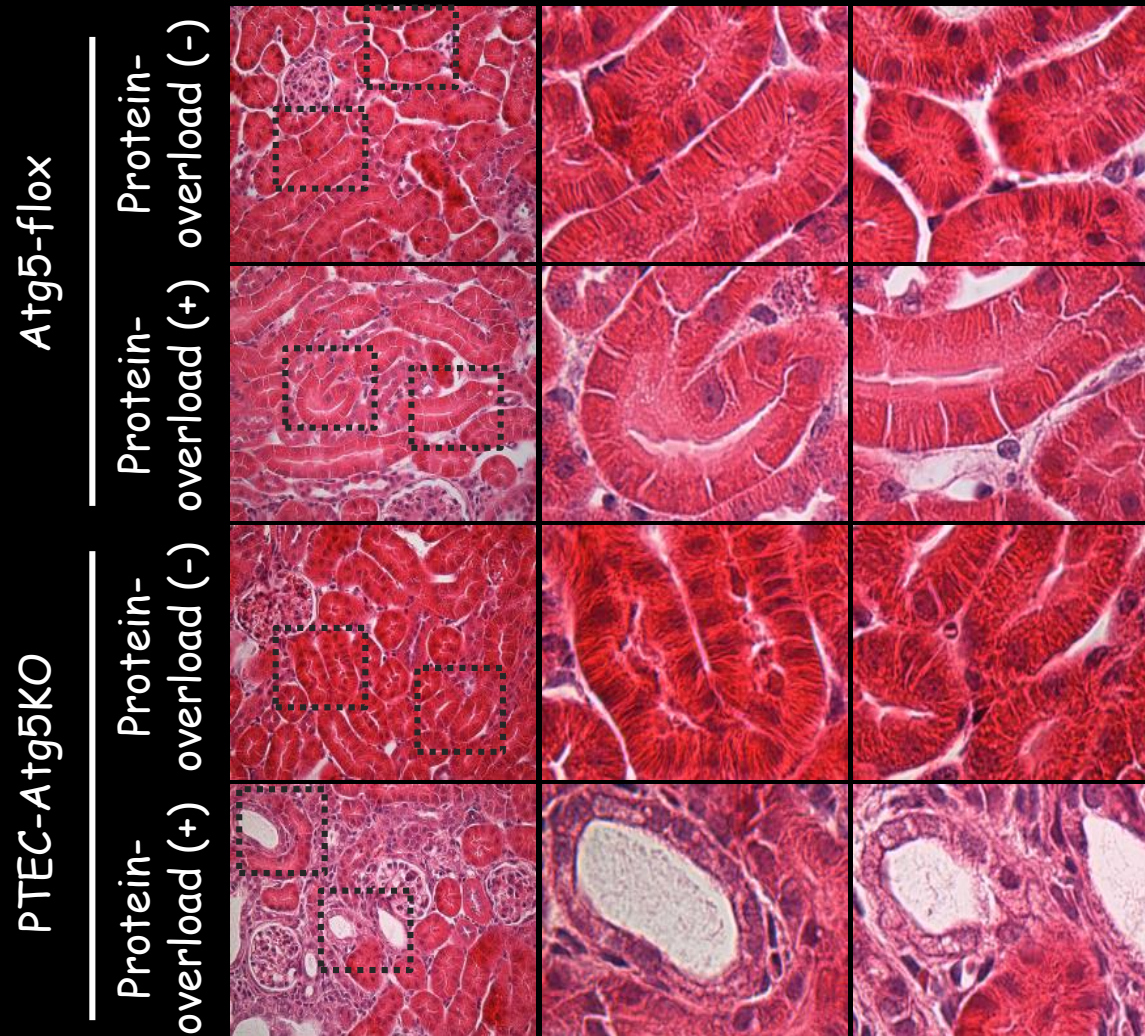
PTEC-Atg5KO



Protein-overload (0.3g/kg/day) 11 days

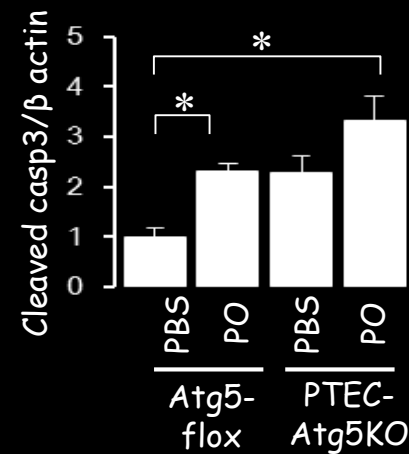
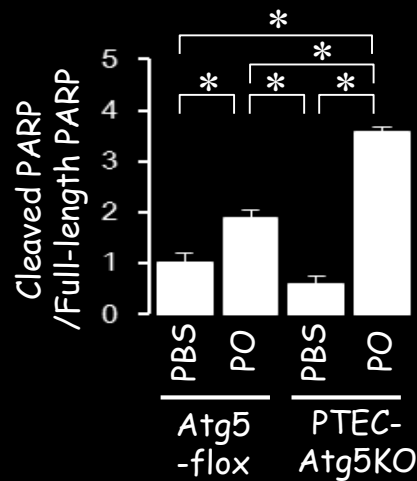
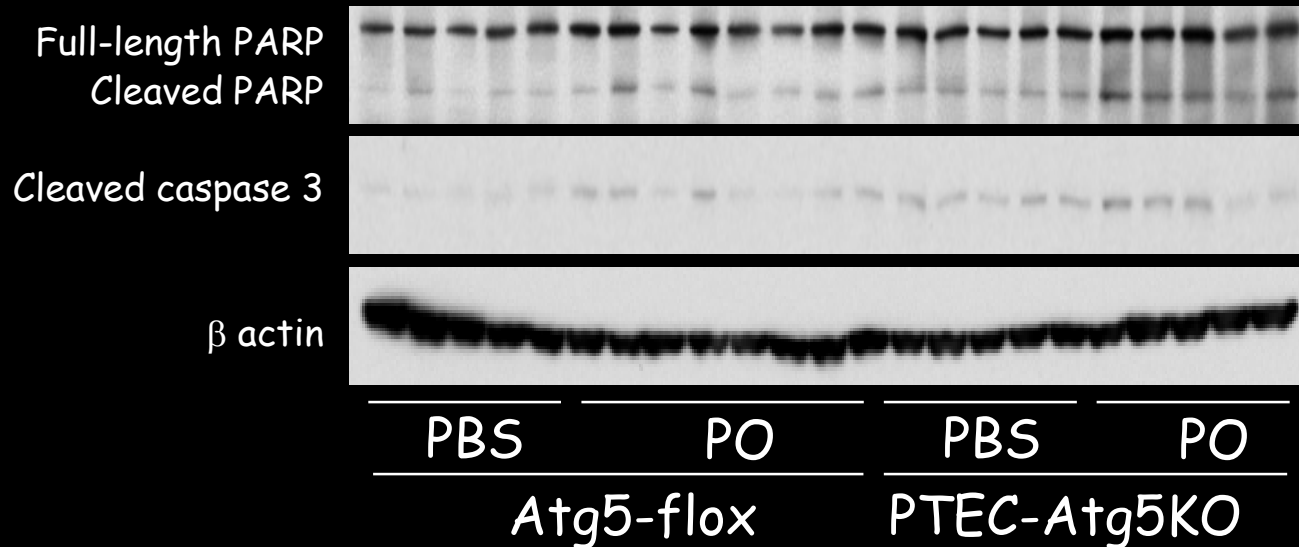
PTEC-Atg5KO

Autophagy-deficiency exacerbated proteinuria-induced tubular cell damages

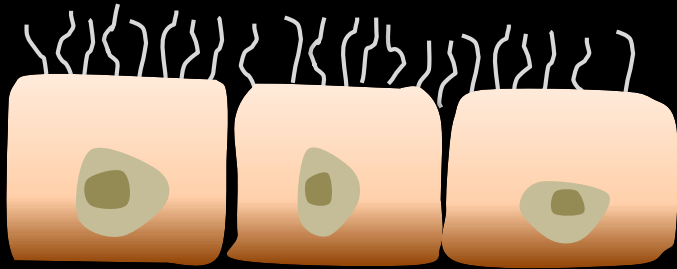


* $P < 0.05$

Autophagy-deficiency exacerbated proteinuria-induced tubular cell apoptosis



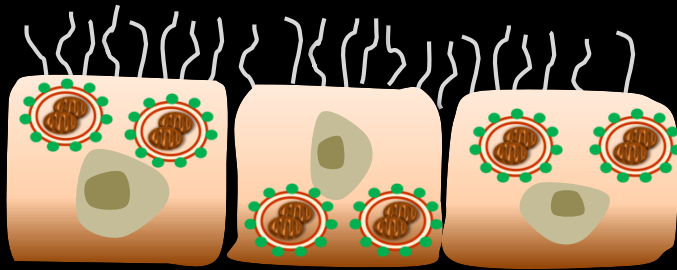
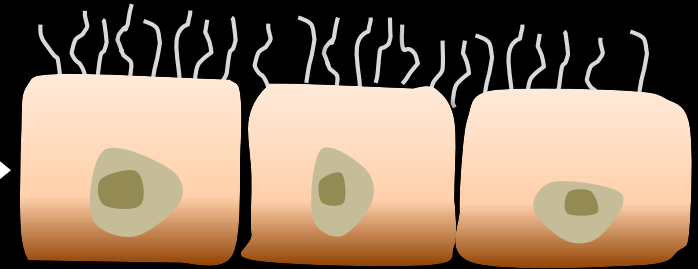
Normal



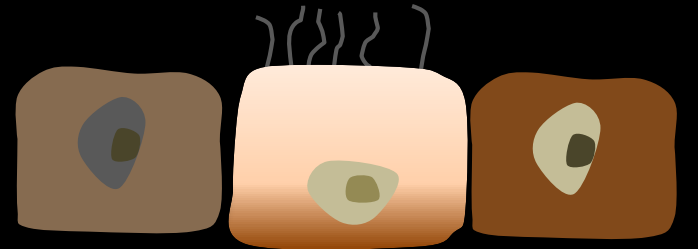
<Stress>
Proteinuria



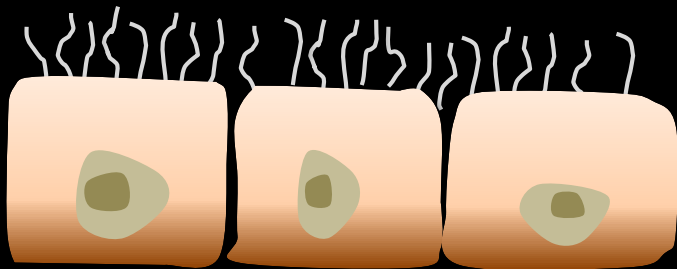
Obese & Diabetes



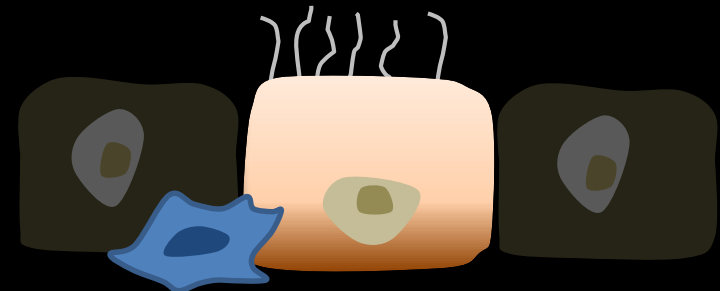
Up-regulation of autophagy
enhances stress resistance



Down-regulation of autophagy
increases stress susceptibility

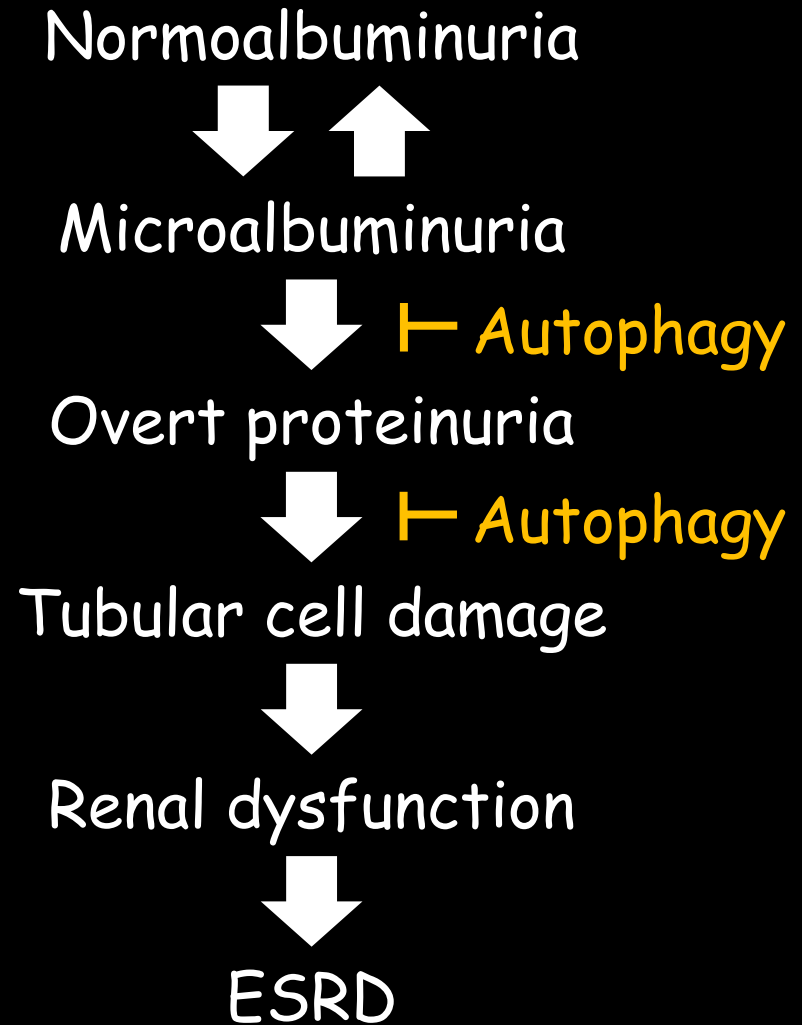
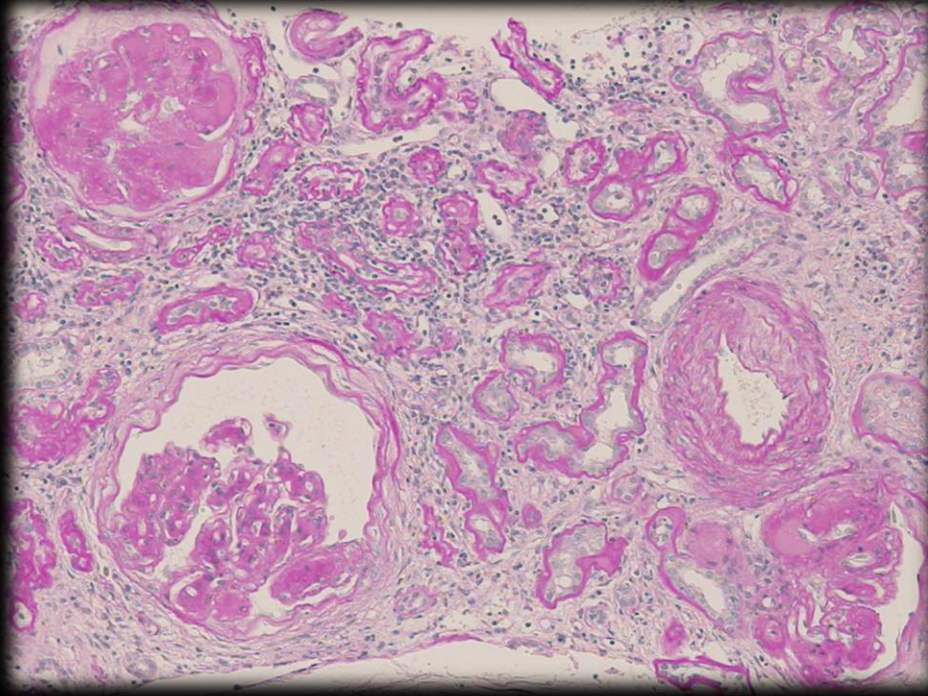


Tissue protection



Tissue damage

Therapeutic roles of autophagy in diabetic nephropathy



Discussion 1

Hyperglycemia

- Activation of DAG-PKC pathway
- Accumulation of AGE
- Alteration of polyol pathway
- Alteration of hexosamine pathway
- ROS production

Lipid abnormality

- High LDL-Cholesterol
- High FFAs

Hemodynamic alterations

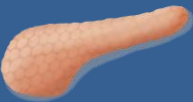
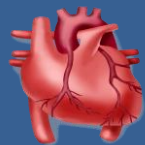
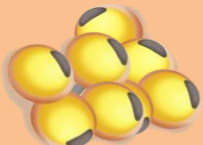
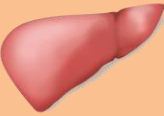
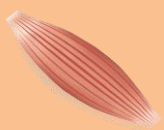
- Renin angiotensin system (RAS)

Calorie restriction mimetics

- Autophagy activation

Discussion 2

- Is autophagy activation good for all diabetic patients?

Damaged organs	Kidney		Atg5 deletion (Proximal tubule) Atg5 deletion (Podocyte)	Tissue-protective roles
	β cell		Atg7 deletion	
	Heart		Atg5 deletion	
Insulin-sensitive organs	Adipocyte		Atg5 deletion Atg7 deletion	Anti-obesity & diabetes
	Liver		Atg7 deletion	
	Skeletal Muscle		Atg7 deletion	

- Biomarkers to detect whole body autophagy activity in human samples.
- Specific activators of autophagy.

Conclusion

Autophagy activation could serve as an additional therapeutic option to prevent diabetic nephropathy.