Supplementary Material

Supplemental Figure Legends

Figure S1 Effects of IAPP peptide on INS-1 cells. (**A**) INS-1 cells were cultured in the presence of the indicated concentrations (0-8 μM) of rIAPP or hIAPP peptide for 48 hr. The number of cells that did not stain with Trypan Blue was counted. Bars represent cell viability (%) compared with the control (0 μM IAPP). Data are the average results of three separate experiments. **p<0.01, rIAPP vs hIAPP. (**B**) Protein levels of cleaved caspase-3 (cl. caspase-3), caspase-3 and actin were assessed by western blotting using INS-1 cells cultured in 8 μM hIAPP (H) peptide or rIAPP (R).

Figure S2 Recombinant adenoviruses expressing hIAPP induces apoptosis in INS-1 cells. (**A**) INS-1 cells were cultured in the presence of the recombinant adenovirus expressing hIAPP or rIAPP for 72 hr. The number of cells that did not stain with Trypan Blue was counted. Bars represent cell viability (%) compared with the rIAPP. Data are the average results of three separate experiments. *p<0.05, rIAPP vs hIAPP. (**B**) Protein levels of cleaved caspase-3 (cl. caspase-3), caspase-3 and Actin were assessed by western blotting using INS-1 cells expressing hIAPP or rIAPP for 48 hr.

Figure S3 Autophagy induction by hIAPP. (**A**) INS-1 cells treated for 12hr with rIAPP or hIAPP peptide. Immunofluorescence was performed using anti-LC3 antibody. (B) Bar graph represents the number of LC3 dots per cell. Scale bars = 10 μm. **p<0.01,

hIAPP vs rIAPP.

Figure S4 Autophagy induction by recombinant adenovirus expressing hIAPP. INS-1 cells were cultured in the presence of the recombinant adenovirus expressing hIAPP or rIAPP for 36 hr. Protein levels of LC3, p62 and GAPDH were assessed by western blotting. To visualize accumulation of LC3-II, the lysosomal inhibitors pepstatin A and E64d were added to the culture medium for 3 hr.

Figure S5 Autophagy induction by hIAPP. Pancreatic islets were isolated from 23-week-old *Atg7*$^{f/f}$, *Atg7*$^{f/f}$*:Cre*, *hIAPP:Atg7*$^{f/f}$, *hIAPP:Atg7*$^{f/f}$*:Cre* mice. Cell lysates were subjected to immunoblot analysis of LC3, p62 and GAPDH.

Figure S6 Effects of human / rat IAPP and autophagy deficiency on viability of INS-1 cells. Atg7-KD INS-1 cells were cultured in the adenovirus expressing rIAPP or hIAPP for 72 hr. The number of cells not stained with Trypan Blue was counted. Bars represent cell viability (%) relative to the rIAPP. *p<0.01, (WT rIAPP vs WT hIAPP), **p<0.05, (*Atg7*-KD rIAPP vs *Atg7*–KD hIAPP), †p<0.01 (WT rIAPP vs *Atg7*–KD rIAPP), ††p<0.01 (WT hIAPP vs *Atg7*–KD hIAPP).

Figure S7 Blood glucose concentrations during IPGTT in 8-week-old standard-diet-fed mice. *Atg7*$^{f/f}$ (n=19), *Atg7*$^{f/f}$*:Cre* (n=17), *hIAPP:Atg7*$^{f/f}$ (n=40), *hIAPP:Atg7*$^{f/f}$*:Cre* (n=31). Data are mean ± SEM. *p<0.05, **p<0.01 (*Atg7*$^{f/f}$ vs*Atg7*$^{f/f}$*:Cre*), †p<0.05, ††p<0.01 (*hIAPP:Atg7*$^{f/f}$ vs *hIAPP:Atg7*$^{f/f}$*:Cre*).

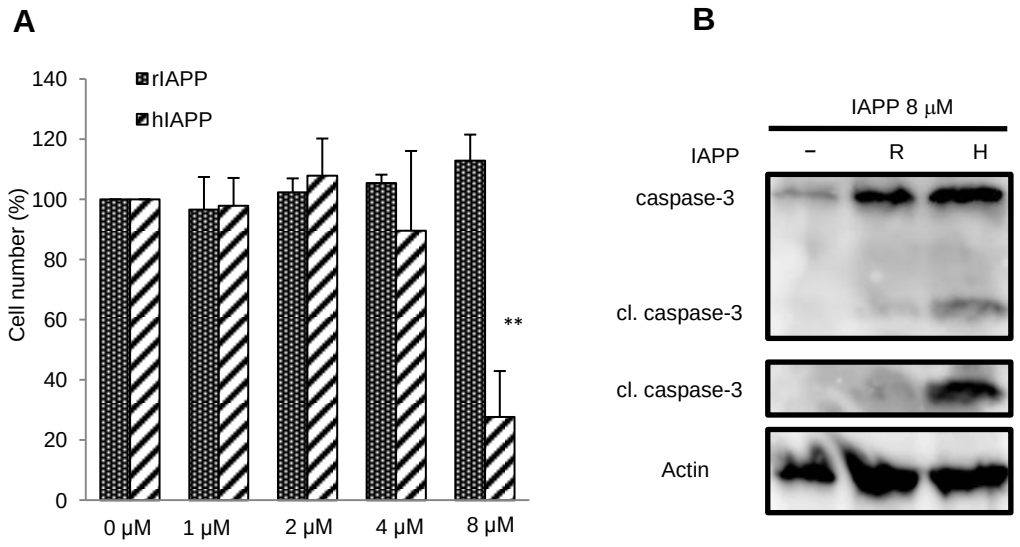
Figure S8 Plasma Insulin levels of the four group during IPGTT (A and B) in 20-week-old standard diet (A) and high fat diet (B). Data are mean ± SEM. *p<0.05, **p<0.01 (*Atg7*$^{f/f}$ vs *Atg7*$^{f/f}$*:Cre*), †p<0.05, †† p<0.01 (*hIAPP:Atg7*$^{f/f}$ vs *hIAPP:Atg7*$^{f/f}$*:Cre*), $^{\#}$p<0.05, $^{\#\#}$p<0.01 (*Atg7*$^{f/f}$ vs *hIAPP:Atg7*$^{f/f}$), ¶p<0.05, ¶¶p<0.01 (*Atg7*$^{f/f}$*:Cre* vs *hIAPP:Atg7*$^{f/f}$*:Cre*).

Figure S9 Blood glucose concentrations during intraperitoneal insulin tolerance test (ITT) in standard diet-fed mice (A) and high-fat-diet-fed mice (B).

Figure S10 Insulin secretion induced by glucose in batch-incubated pancreatic islets isolated from 22-week-old high-fat-diet-fed mice. Data are mean ± SEM. **p<0.01 (*Atg7*$^{f/f}$*:Cre* vs *hIAPP:Atg7*$^{f/f}$*:Cre*), †† p<0.01 (*hIAPP:Atg7*$^{f/f}$ vs *hIAPP:Atg7*$^{f/f}$*:Cre*).

Figure S11 Amyloid stain. Positive controls are section from amyloidosis of human kidney and human diabetic pancreas. Pancreatic tissue sections from *hIAPP:Atg7*$^{f/f}$ and *hIAPP:Atg7*$^{f/f}$*:Cre* mice were stained with congo red (A), direct fast scarlet (B) and thioflavin S (C). Scale bars =100 μm.

Supplemental Data



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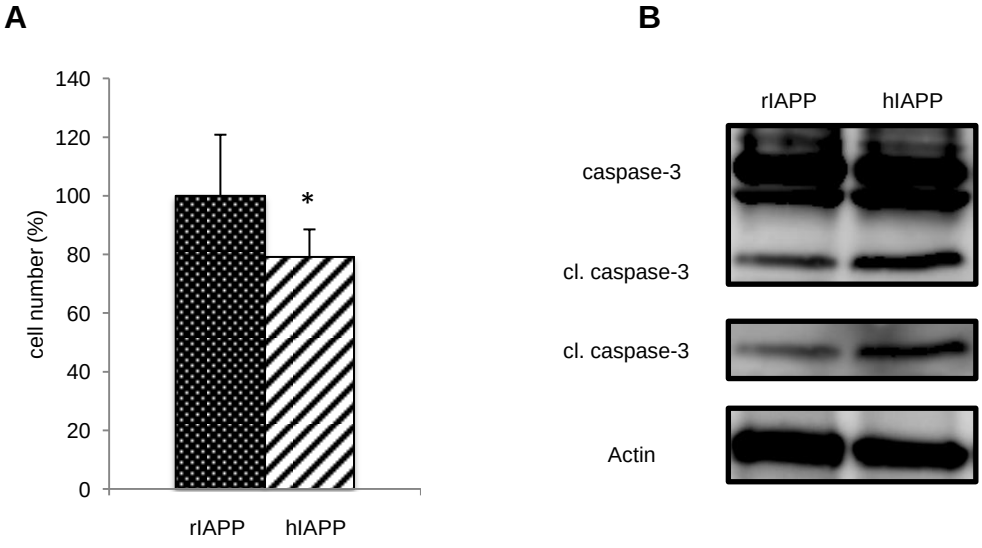

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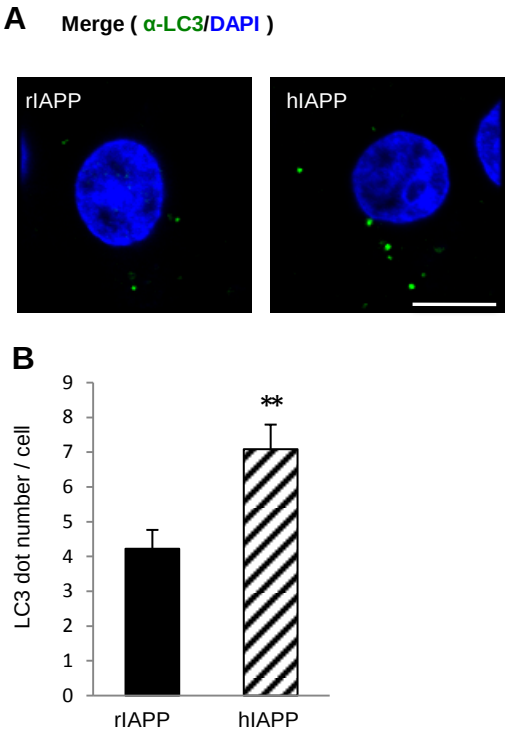

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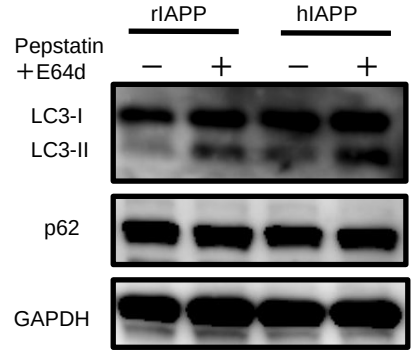
Autophagy induction by hIAPP. (**A**) INS-1 cells treated for 12hr with rIAPP or hIAPP peptide. Immunofluorescence was performed using anti-LC3 antibody. (**B**) Bar graph represents the number of LC3 dots per cell. Scale bars = 10 μm. **p<0.01, hIAPP vs rIAPP.



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Autophagy induction by recombinant adenovirus expressing hIAPP. INS-1 cells were cultured in the presence of the recombinant adenovirus expressing hIAPP or rIAPP for 36 hr. Protein levels of LC3, p62 and GAPDH were assessed by western blotting. To visualize accumulation of LC3-II, the lysosomal inhibitors pepstatin A and E64d were added to the culture medium for 3 hr.

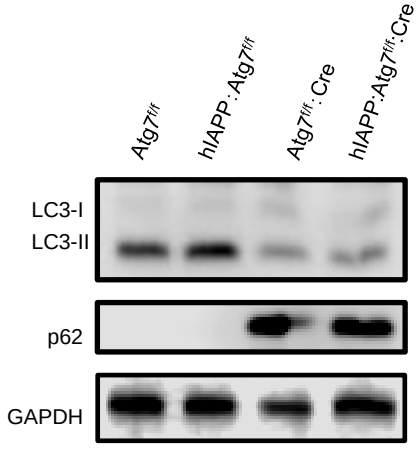
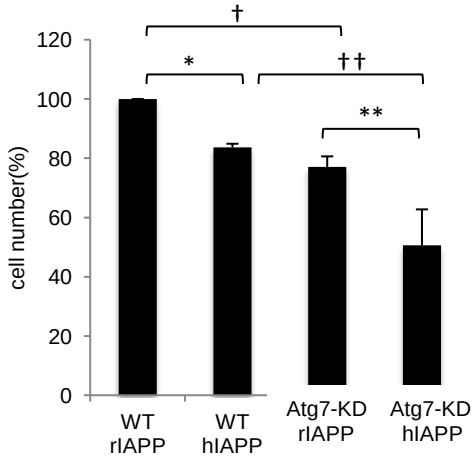


Figure S5
Autophagy induction by hIAPP. Pancreatic islets were isolated from 23-week-old *Atg7*$^{f/f}$, *Atg7*$^{f/f}$*:Cre*, *hIAPP:Atg7*$^{f/f}$, *hIAPP:Atg7*$^{f/f}$*:Cre* mice fed standard diet. Cell lysates were subjected to immunoblot analysis of LC3, p62 and GAPDH.



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Effects of human / rat IAPP and autophagy deficiency on viability of INS-1 cells. Atg7-KD INS-1 cells were cultured in the adenovirus expressing rIAPP or hIAPP for 72 hr. The number of cells not stained with Trypan Blue was counted. Bars represent cell viability (%) relative to the rIAPP. *p<0.01, (WT rIAPP vs WT hIAPP), **p<0.05, (*Atg7*-KD rIAPP vs *Atg7*–KD hIAPP), †p<0.01 (WT rIAPP vs *Atg7*–KD rIAPP), ††p<0.01 (WT hIAPP vs *Atg7*–KD hIAPP) .

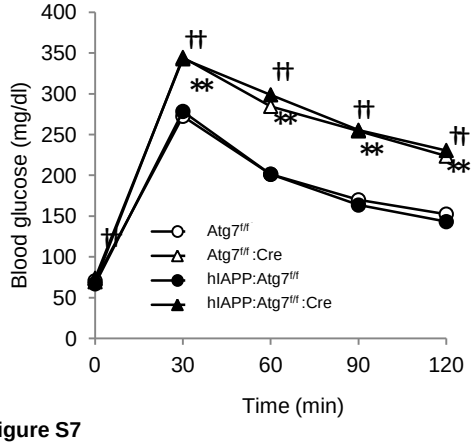


Figure S7
Blood glucose concentrations during IPGTT in 8-week-old standard-diet-fed mice. *Atg7$^{f/f}$* (n=19), *Atg7$^{f/f}$:Cre* (n=17), *hIAPP:Atg7$^{f/f}$* (n=40), *hIAPP:Atg7$^{f/f}$:Cre* (n=31). Data are mean ± SEM. *p<0.05, **p<0.01 (*Atg7$^{f/f}$* vs*Atg7$^{f/f}$:Cre*), †p<0.05, ††p<0.01 (*hIAPP:Atg7$^{f/f}$* vs *hIAPP:Atg7$^{f/f}$:Cre*).

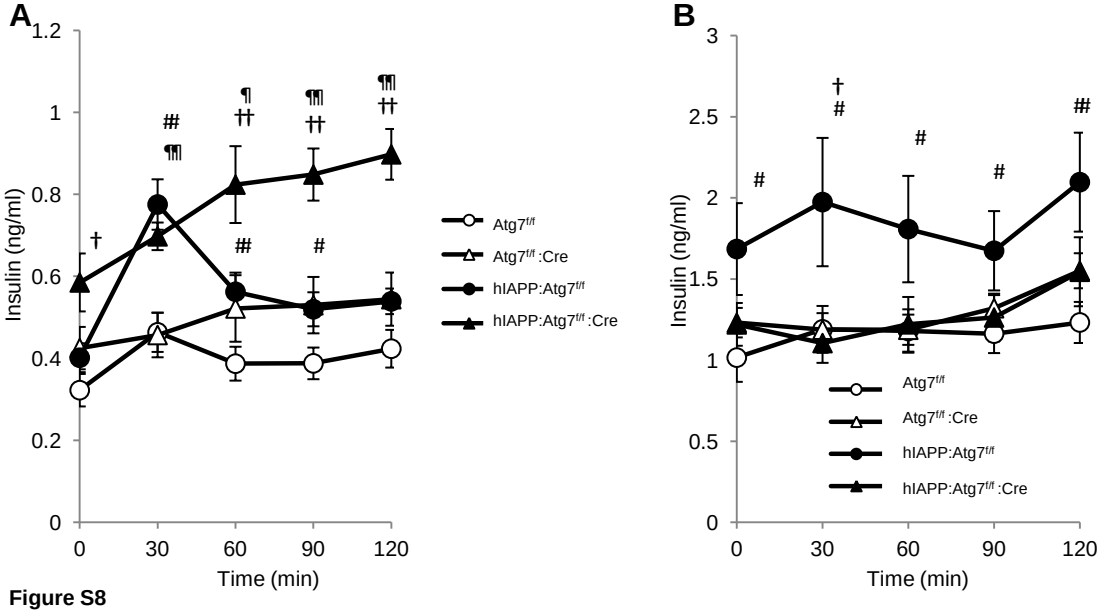


Figure S8
Plasma Insulin levels of the four group during IPGTT(**A** and **B**) in 20-week-old mice fed standard diet (**A**) and high fat diet **(B)**. Data are mean ± SEM. *p<0.05, **p<0.01 (*Atg7$^{f/f}$* vs *Atg7$^{f/f}$:Cre*), †p<0.05, †† p<0.01 (*hIAPP:Atg7$^{f/f}$* vs *hIAPP:Atg7$^{f/f}$:Cre*), #p<0.05, ##p<0.01 (*Atg7$^{f/f}$* vs *hIAPP:Atg7$^{f/f}$*), ¶p<0.05, ¶¶p<0.01 (*Atg7$^{f/f}$:Cre* vs *hIAPP:Atg7$^{f/f}$:Cre*).

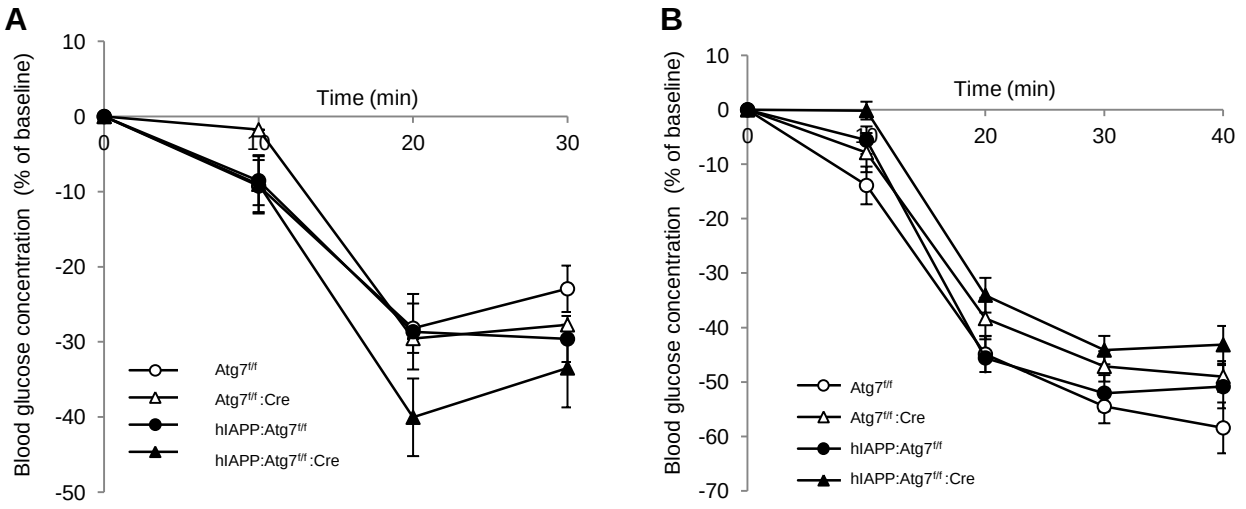


Figure S9
Blood glucose concentrations during intraperitoneal insulin tolerance test (ITT) in standard diet-fed mice (**A**) and high-fat diet-fed mice (**B**).

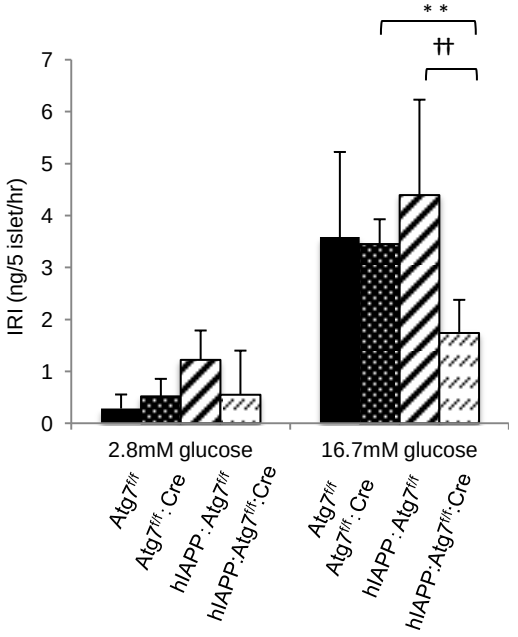
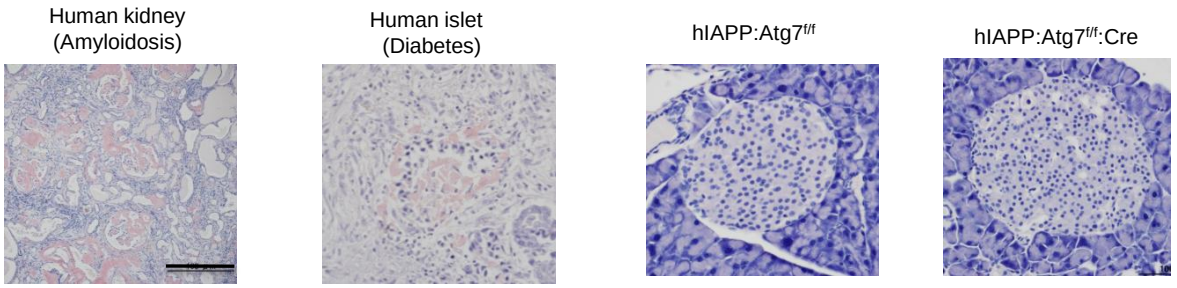


Figure S10
Insulin secretion induced by glucose in batch-incubated pancreatic islets isolated from 22-week-old high-fat-diet-fed mice. Data are mean ± SEM. **p<0.01 (*Atg7$^{f/f}$:Cre* vs *hIAPP:Atg7$^{f/f}$:Cre*), †† p<0.01 (*hIAPP:Atg7$^{f/f}$* vs *hIAPP:Atg7$^{f/f}$:Cre*).

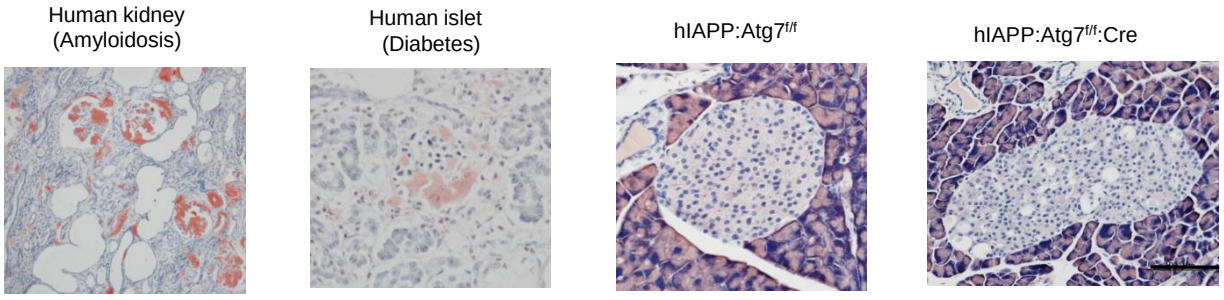
A

Congo Red Stain



B

Direct Fast Scarlet stain



C

Thioflavin-S Stain

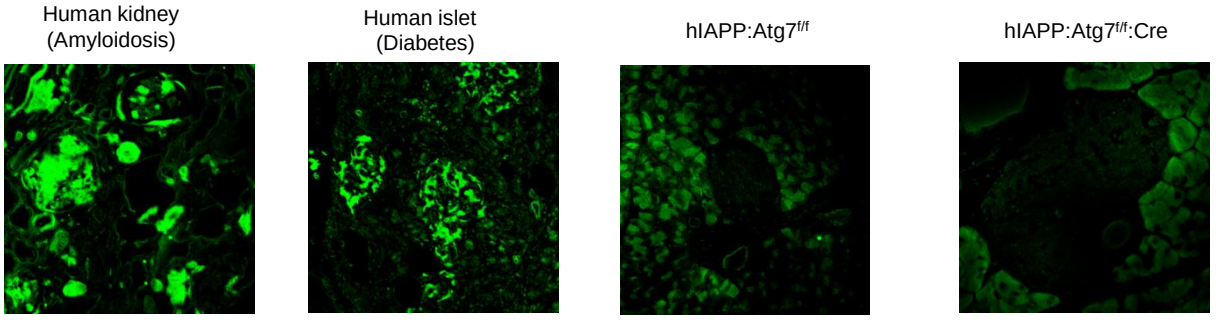


Figure S11
Amyloid stain. Positive controls are section from amyloidosis of human kidney and human diabetic pancreas. Pancreatic tissue sections from *hIAPP:Atg7$^{f/f}$* and *hIAPP:Atg7$^{f/f}$:Cre* mice were stained with congo red (**A**), direct fast scarlet (**B**) and thioflavin S (**C**). Scale bars =100 μm.