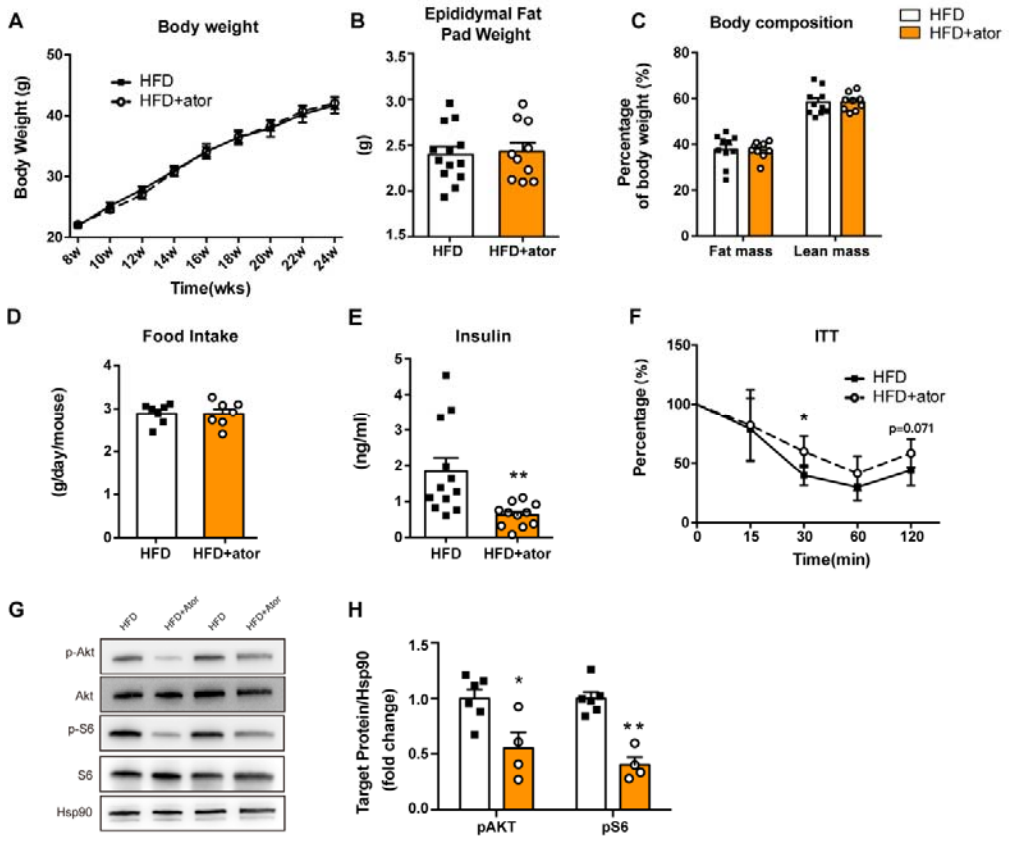
SUPPLEMENTARY DATA

Supplementary Table 1. Primer List for qRT-PCR (mouse)

Gene	5'-Forward Primer-3'	5'-Reverse Primer-3'
Gck	CCGTGATCCGGGAAGAGAA	GGGAAACCTGACAGGGATGAG
Glut2	TCAGAAGACAAGATCACCGGA	GCTGGTGTGACTGTAAGTGGG
MafA	TTCAGCAAGGAGGAGGTCAT	CTCTGGAGCTGGCACTTCTC
MafB	CTGCGCCCCTAGCCCTGGACTC	GGCGGCCCTGGCACTCACAAA
Nkx6.1	GAAGCGTGGTGTTGAGATGA	GGGCCCTTCCAAACAAGT
Gapdh	CATGTTCCAGTATGACTCCACTC	GGCCTCACCCCATTTGATGT
Ldlr	TGACTCAGACGAACAAGGCTG	ATCTAGGCAATCTCGGTCTCC
Hmgcs1	AACTGGTGCAGAAATCTCTAGC	GGTTGAATAGCTCAGAACTAGCC
Srebp2	CAGGTGCAGACGGTACAGG	CGTGGTCAACACAAGGGAATC
Hmgcr	AGCTTGCCCGAATTGTATGTG	TCTGTTGTGAACCATGTGACTTC
Npc1	AGTGTTCATATCTACGAACCGTACC	TCAATGGCGATCTGTAAGTCC
Abcg1	CTTTCCTACTCTGTACCCGAGG	CGGGGCATTCCATTGATAAGG
Abca1	CGTTTCCGGGAAGTGTCCTA	GCTAGAGATGACAAGGAGGATGG
Lxrα	CGACAGAGCTTCGTCCACAA	GCTCGTTCCCCAGCATTTT
Lxrβ	CGTGCCTGGGAATGGTTCT	AGTCTCCTGCCCCTCTTCCTT
Rab5a	AAGCACAGTCCTATGCAGATGAC	GCTGAGTTTGCACCAGGATTCTG
Rabggtb	CTTCAGTCTTTCGGCGGTCG	CGCCGCTCATTCTCAGGTAT
Atp6ap2	TCACATTGCGGCAGCTCCGTAA	GTAGCACTTGCAGTTCGGAGAG
Ctsl	GGAAAATGGAGGTCTGGACTCG	GTGTCATTAGCCACAGCGAACTC
Cab39	TCCGAGACAAGAGCCGCAACAT	GAGGAACTCGATGAGCTTGGTC
Scg2	CAGGAAGAGGTGAGAGACAGCA	TGGAGGCATCCTCTGAGAGTTG
Akt3	GAGATGGATGCGTCTACAACCC	TCCACTTGCCTTCTCTCGAACC
Gjd2	GTGGTGCTCAATCTGGCTGAAC	GACTGAGTCCTGCCGAAATTGG
Mapk1	TCAAGCCTTCCAACCTCCTGCT	AGCTCTGTACCAACGTGTGGCT
Vamp4	TCGGATAATGCCACCGCTTTCAG	CATTAGCAAAAGGATCGCTGCAG
Ulk2	GAGGACGAAGACTCTCTACTGG	GAGTGCCTACTCCTGGCTTCAT
Tsc2	GAGCAGTATGCCAGCGTGTTTG	GCACCTGATGAACCACATGGCT
Pcolce	GAGTGACGACTCAAAGAGGCTG	AAGCCATCTGCGGTGACACTGA
Psck1	GGAGAGAATCCTGTAGGCACCT	GCTCTGGTTGAGAAGATGTCCC

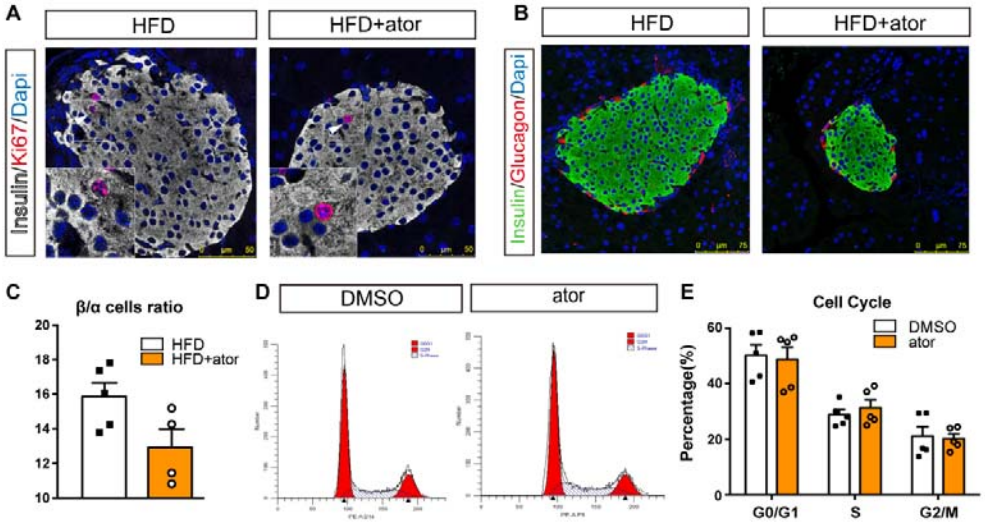
SUPPLEMENTARY DATA

Supplementary Figure S1. Metabolic phenotypes of HFD mice after 4 months of treatment.
A: Alterations in mouse body weight during the 16-week period (n = 11). **B**: Epididymal fat pad weight (n=10-13). **C**: Body composition (n=9-10). **D**: Food intake (n=7). **E**: Fasting insulin level (n=11-12). **F**: Insulin tolerance test (n=5), in the end of the study. **G**: Representative Western blot images of liver samples for pS6 S240/244 and pAkt S473 levels. **H**: Densitometry quantification of the bands in G (n=4-6). Data are presented as the mean ± S.E.M, *P < 0.05, unpaired two-tailed Student's t test.



SUPPLEMENTARY DATA

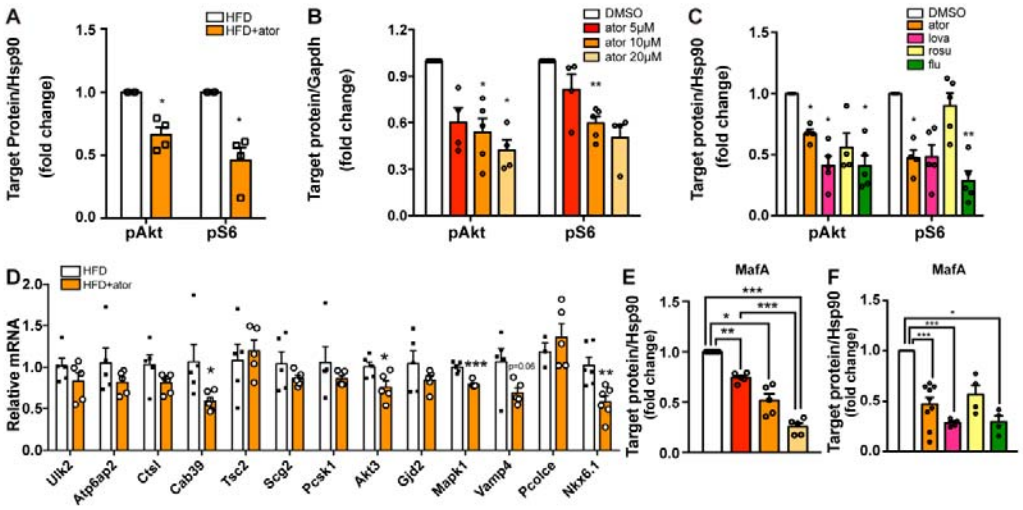
Supplementary Figure S2. Islet β-cell proliferation and proportion after ator treatment.
A: Representative immunofluorescence images of islets stained for Ki67 (red), insulin (white) and DAPI (blue). Original magnification, ×630 (n=5-6, 50−70 islets per animal). **B**: Representative immunofluorescence images of islets stained for glucagon (red), insulin (green) and DAPI (blue). Original magnification, ×400 (n=5-6, 50−70 islets per animal). **C**: β/α cell ratio (n=4-5, 50−70 islets per animal, more than 3000 β-cells were counted). **D**: Cell cycle analysis in MIN6 cells (n=5). **E**: Quantification of the proportion of cells in the G0/G1, S and G2/M phase of the cell cycle after ator treatment in MIN6 cells (n=5). Data are presented as the mean ± S.E.M, *P < 0.05, unpaired two-tailed Student's t test.



SUPPLEMENTARY DATA

Supplementary Figure S3. Quantification of mTOR signaling and key pancreatic TF alterations refer to Fig. 3 and 4.

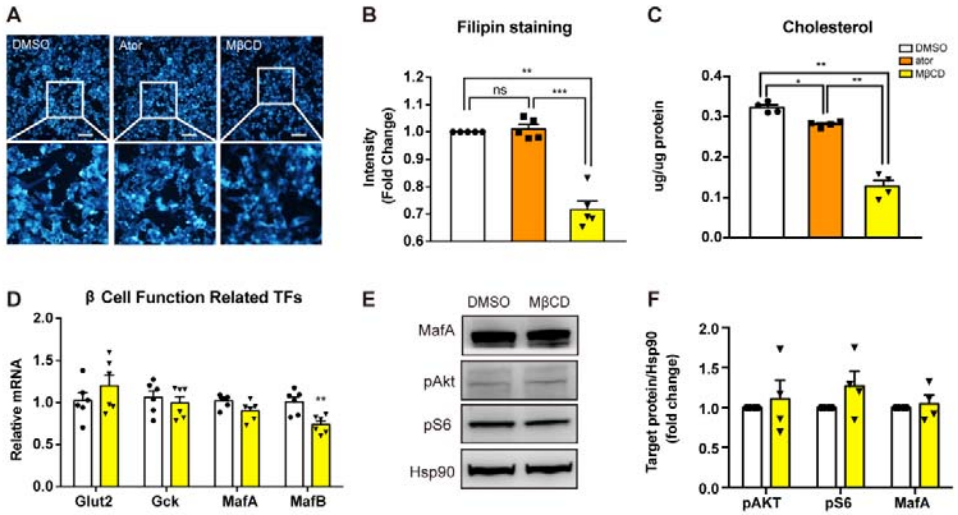
Densitometry quantification of the Western blot bands for pS6 S240/244 and pAkt S473 is as follows: **A**: Mouse islets in Fig. 3G (n=4). **B**: MIN6 cells in Fig. 3H (n=4-5). **C**: MIN6 cells in Fig. 3I (n=4-5). **D**: Relative mRNA expression of Ulk2, Atp6ap2, Ctsl, Cab39, Tsc2, Scg2, Psck1, Akt3, Gjd2, Mapk1, Vamp4, Pcolce, Nkx6.1 in islets by RT-PCR (n=5-6). Densitometry quantification of the Western blot bands for MafA in MIN6 cells is as follows: **E**: Fig.4E (n=5) and **F**: Fig.4F (n=4-9). Ator: atorvastatin; lova: lovastatin; rosu: rosuvastatin; flu: fluvastatin. Data are presented as the mean ± S.E.M, *P < 0.05, **P < 0.01; unpaired two-tailed Student's t test.



SUPPLEMENTARY DATA

Supplementary Figure S4. **The effect of decreased intracellular cholesterol levels on mTOR signaling and key TFs in pancreatic β-cell.**

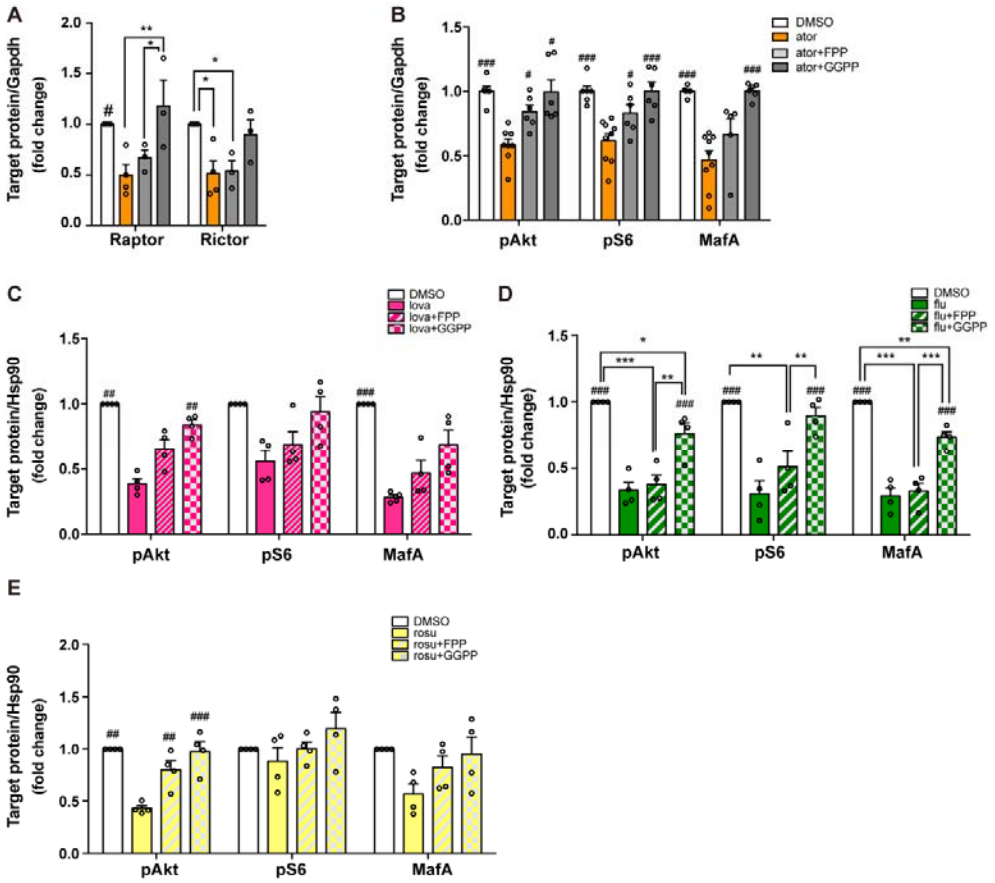
A: Representative images of filipin staining (blue, original magnification, ×200) after 24 hours of atorvastatin, MβCD and vehicle treatment. Scale bars, 200 μm, (n=5). **B**: Filipin staining and intensity quantification in MIN6 cells after 24 hours of atorvastatin, MβCD and vehicle treatment (n=5). **C**: Intracellular cholesterol levels in MIN6 cells (n=4). **D**: RT-PCR analysis of key islet gene expression changed by MβCD treatment (n=6). **E**: Representative images and **F**: densitometry quantification of Western blotting for MafA, pS6 S240/244 and pAkt S473 levels in MIN6 cells after MβCD or vehicle treatment (n=4). Data are presented as the mean ± S.E.M, * $P < 0.05$, **$P < 0.01$, ns=not statistically significant; unpaired two-tailed Student's t test, one-way ANOVA for three groups.



SUPPLEMENTARY DATA

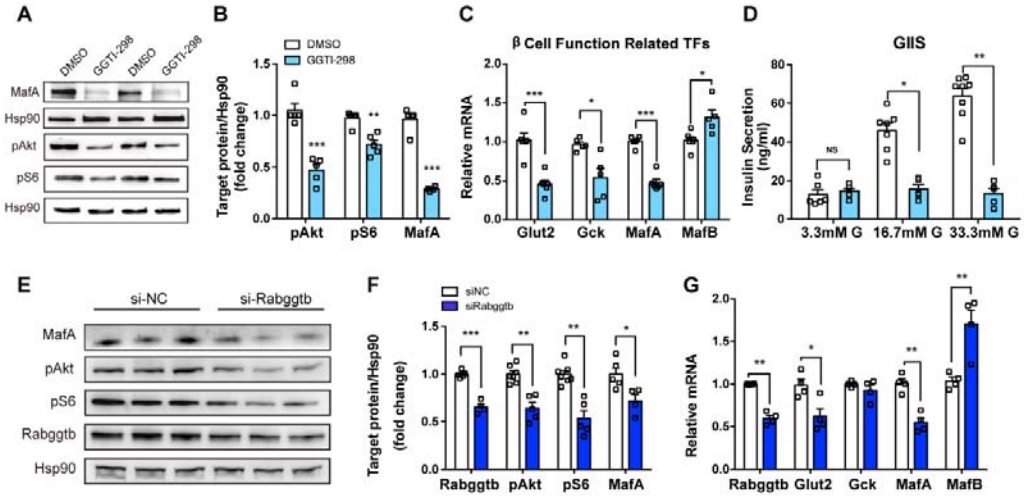
Supplementary Figure S5. **GGPP can reverse the inhibitory effect of statins on mTOR and pancreatic TFs.**

A: Densitometry quantification of the Western blot bands for Rictor and Raptor of MIN6 cells, in Fig.5B (n=3-4). Densitometry quantification of the Western blot bands for pAKT, pS6 and MafA of MIN6 cells in **B**: Fig. 5C (n=5-9), **C**: Fig. 5G (n=4), **D**: Fig. 5J (n=4), **E**: Fig. 5M (n=4). Data are presented as the mean ± S.E.M, * $P < 0.05$, **$P < 0.01$, ***$P < 0.001$; $^{\#}$ $P < 0.05$ $^{\#\#}$ $P < 0.01$ $^{\#\#\#}$ $P < 0.001$ vs ator; unpaired two-tailed Student's t test, one-way ANOVA for four groups.



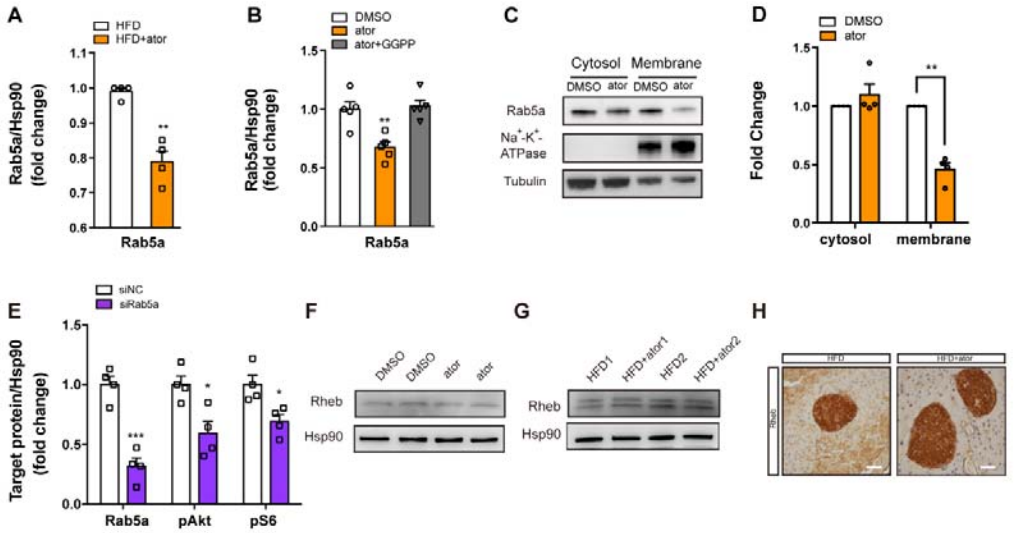
SUPPLEMENTARY DATA

Supplementary Figure S6. GGTase inhibition mimicked the effects of statins on β cells.
A: Representative images and **B**: densitometry quantification of the bands for pAkt S473, pS6 S240/244 and MafA in MIN6 cells after GGTI-298 incubation for 24 hours (n=5). **C**: mRNA levels of *Glut2, Gck, MafA* and *MafB* after 24 hours of GGTI-298 treatment (n=5). **D**: *In vitro* GIIS of $3x10^5$ MIN6 cells pretreated with GGTI-298 or vehicle (n=4-8). **E**: Representative images and **F**: densitometry quantification of the bands for MafA, pAkt S473, pS6 S240/244 and Rabggtb in MIN6 cells following *Rabggtb* knockdown (n=4-5). **G**: mRNA expression levels of *Rabggtb*, *Glut2, Gck, MafA* and *MafB* following *Rabggtb* knockdown in MIN6 cells (n=4). Data are presented as the mean ± S.E.M, * P < 0.05, **P < 0.01; unpaired two-tailed Student's t test.



SUPPLEMENTARY DATA

Supplementary Figure S7. Responses of β-cell Rab5a and Rheb to ator treatment.
Densitometry quantification of the bands for Rab5a protein levels in **A**: pancreatic islets in Fig. 6B (n=4) and **B**: MIN6 cells in Fig. 6F (n=5). **C**: Representative images and **D**: band densitometry quantification of the Western blots for Rab5a in the cytosol and membrane fractions after ator treatment (10 μM) (n=4). **E**: Densitometry quantification of the Western blot bands for Rab5a, pAkt S473 and pS6 S240/244 following *Rab5a* knockdown in Fig.6H (n=4). Western blots of Rheb **F**: in MIN6 cells (n=4) and **G**: in islets (n=5). **H**: Representative images of immunochemistry staining for Rheb in pancreas section. Scale bars, 100 μm. Data are presented as the mean ± S.E.M, * P < 0.05, **P < 0.01; unpaired two-tailed Student's t test, one-way ANOVA for three groups.



SUPPLEMENTARY DATA

Supplementary Figure S8. Scheme of the hypothetic mechanism underlying the regulation of β-cell functional mass by statins.