Supplementary Information for

Endogenous lipid-GPR120 signaling modulates pancreatic islet homeostasis to different extents

Ya-Qin Du[#1,2], Xue-Ying Sha[#1], Jie Cheng[#2], Jin Wang[#7], Jing-Yu Lin[2], Wen-Tao An[2], Wei Pan[2], Li-Jun Zhang[2], Xiao-Na Tao[3], Yun-Fei Xu[4], Ying-Li Jia[1], Zhao Yang[3], Peng Xiao[3], Ming Liu[5,6], Jin-Peng Sun[1,3] and Xiao Yu*[2]

Jin-Peng Sun (corresponding author)
E-mail: sunjinpeng@bjmu.edu.cn
Xiao Yu (corresponding author)
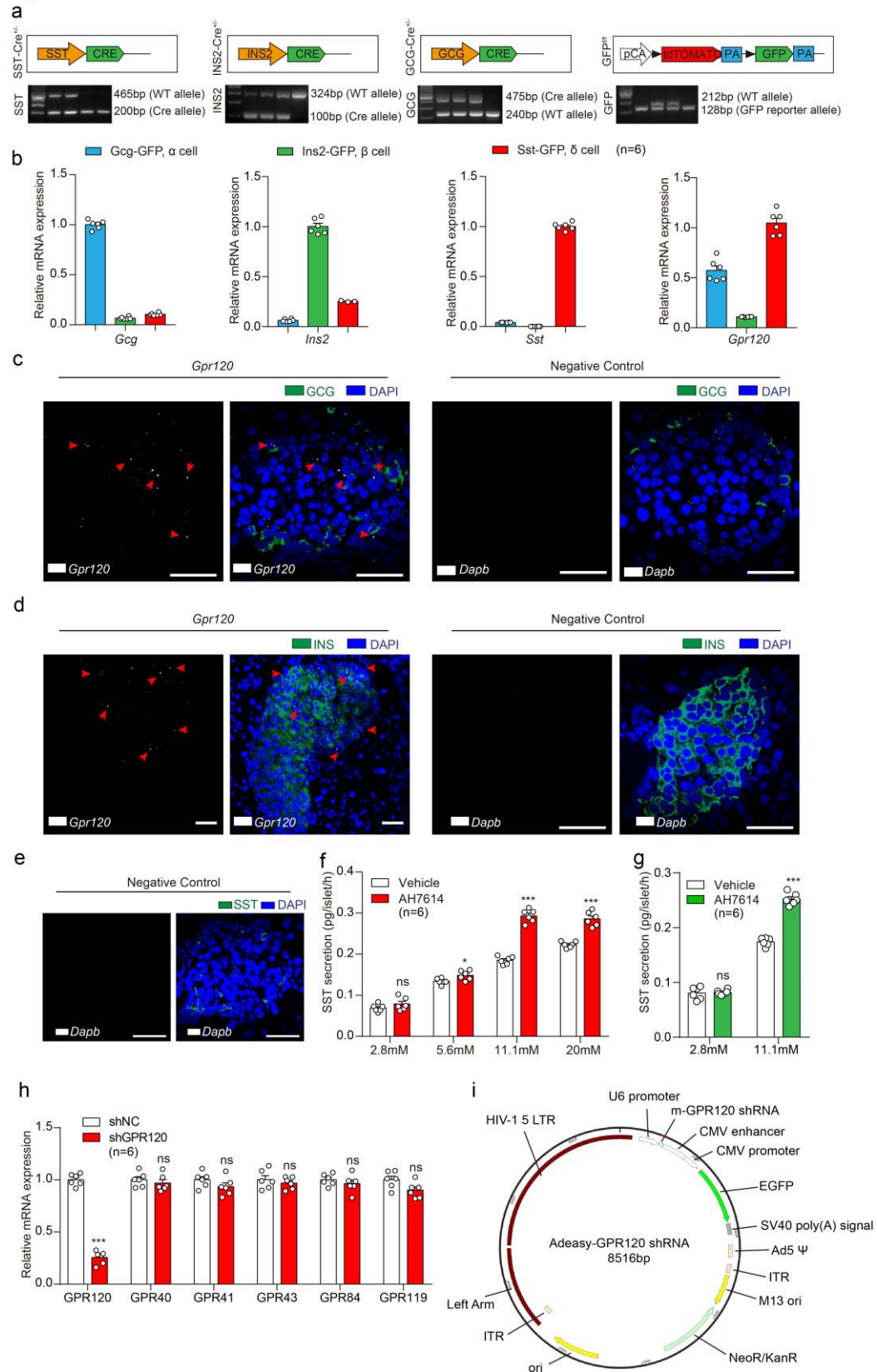E-mail: yuxiao@sdu.edu.cn

This PDF file includes:
Figures S1 to S9
Tables S1 to S2

Fig.S1: Endogenous GPR120 activity in pancreatic islets.

(a) Schematic diagram and PCR analysis of genomic DNA of tails from *Sst-Cre*, *Ins2-Cre*, *Gcg-Cre* and GFP-reporter mice for genotyping.

(b) qRT-PCR analysis of mRNA expression levels of Gcg, Ins2, Sst and Gpr120 in primary α, β and δ cells isolated from pancreatic islets of Ins2-cre$^{+/-}$GFP$^{f/f}$, Gcg-cre$^{+/-}$GFP$^{f/f}$ and Sst-cre$^{+/-}$GFP$^{f/f}$ mice. 800 islets were isolated from 12-14 mice of indicated genotypes. β, α and δ cells were isolated from *ins2-cre$^{+/-}$GFP$^{f/f}$*, *gcg-cre$^{+/-}$GFP$^{f/f}$* and *sst-cre$^{+/-}$GFP$^{f/f}$* mouse islets, respectively. The islets were incubated in EDTA-MKRBB for 10 min at 33°C followed by deposition at room temperature. Then, the islets were incubated in 0.6 U/ml Dispase II for 5 min at 33°C before dispersion into single cells. Hank's buffer was used to wash and resuspend the single cells. Cells with GFP expression were sorted by the FACS service at Shandong University School of Basic Medical Sciences. Data are from six independent experiments(n=6).

(c-d) Representative images of colorimetric RNAscope in situ hybridization for GPR120 (white) and immunostaining of GCG$^+$ pancreatic α cells (green) (c); or immunostaining of INS$^+$ pancreatic β cells (green) (d) in pancreatic sections of WT mice. Scale bar: 50 μm. n = 6 mice per group; 3-5 random areas were selected from each islet section, and 6-8 sections were randomly selected from each mouse. Pancreas tissues from WT mice were fixed overnight in 4% paraformaldehyde at 4°C, dehydrated in sucrose solution and embedded in Tissue-Tek OCT compound. The tissues were sliced into 6-μm-thick sections, and in situ hybridization was performed using an RNA scope 2.5 HD detection kit (red) (Cat. #322360, ACD Bio) according to the manufacturer's instructions. Probes for Gpr120 was customized from ACD Bio. The slices were incubated in blocking buffer after hybridization and incubated overnight at 4°C with primary antibodies. After washing three times with PBS, the slices were incubated at 4°C for 2.5 h with the secondary antibodies. The slices were stained with 4',6'-diamidino-2-phenylindole and subjected to fluorescence microscopic analysis using an LSM780 laser scanning confocal microscope system (ZEISS, Germany).

(e) Negative control of RNAscope in situ hybridization for GPR120 and immunostaining of SST$^+$ pancreatic δ cells (green) in pancreatic sections of WT mice corresponding to Fig.1a.

(f) Different concentration of glucose-induced somatostatin secretion in islets pretreated with or without 30μM AH7614. 400 islets from 7-9 WT mice were grouped (50 islets/group) for somatostatin secretion experiment. Data are from six independent experiments (n=6).

(g) Glucose-induced somatostatin secretion in islets pretreated with or without 30μM AH7614. Human islets were grouped (50 islets/group) for somatostatin secretion experiment. Data are from six independent experiments (n=6)
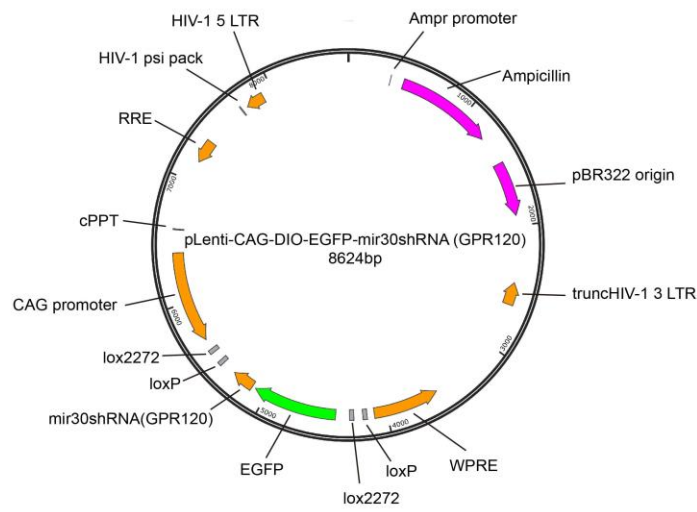
(h) qRT-PCR analysis of mRNA expression levels of GPR120, GPR40, GPR41, GPR43, GPR84 and GPR119 in islets pretreated with adenovirus expressing control or GPR120 shRNA. 200 islets from 2-4 mice of indicated genotypes were grouped (100 islets/group) for RNA extraction. Data are from six independent experiments (n=6).

(i) Plasmid map of Adeasy-GPR120 shRNA used to package GPR120-shRNA adenoviruses obtained from Hanbio Technology Co., Ltd. The specific RNA interference sequence of GPR120 we chose in this study was CCGAUUUGCACAUUGGAUUTT (5'-3').
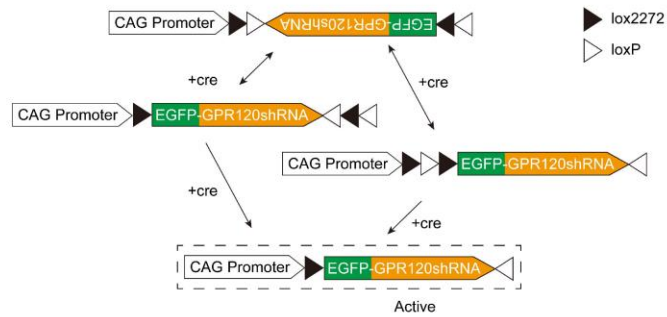
(f-g) $*p<0.05$; $***p<0.001$; ns, no significant difference; islet treated with AH7614 compared with those treated with vehicle; (h) $***p<0.001$; ns, no significant difference; islets pretreated with adenovirus expressing GPR120 shRNA compared with control adenovirus; The bars represent mean ± SEM. All data statistics were analyzed using two-way ANOVA with Dunnett's post hoc test.
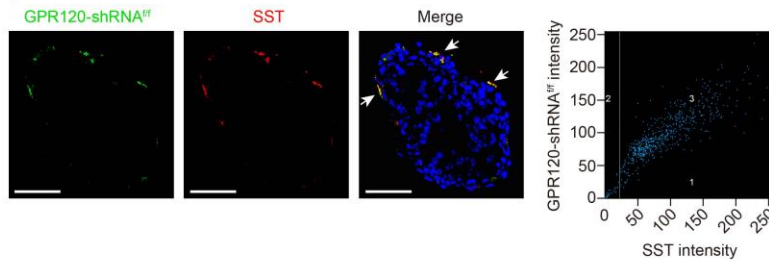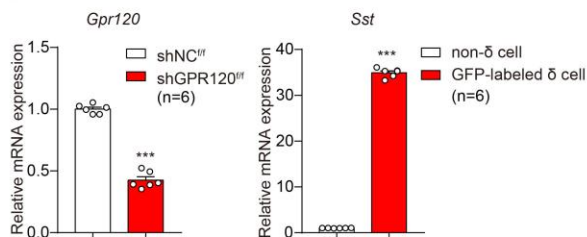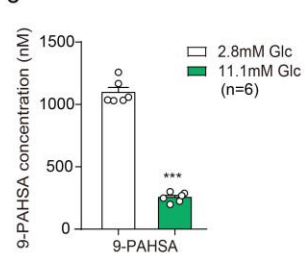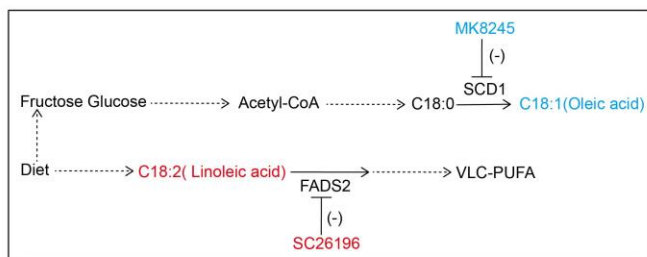
Figure S2

a

pLenti-CAG-DIO-EGFP-mir30shRNA (GPR120)
8624bp

HIV-1 5 LTR
HIV-1 psi pack
RRE
cPPT
CAG promoter
lox2272
loxP
mir30shRNA(GPR120)
EGFP
lox2272
loxP
WPRE
truncHIV-1 3 LTR
pBR322 origin
Ampicillin
Ampr promoter

b

CAG Promoter EGFP-GPR120shRNA

lox2272
loxP

+cre   +cre

CAG Promoter EGFP-GPR120shRNA

CAG Promoter EGFP-GPR120shRNA

+cre   +cre

CAG Promoter EGFP-GPR120shRNA

Active

c

GPR120-shRNA$^{f/f}$ SST   Merge

d

Gpr120

Relative mRNA expression

□ shNC$^{f/f}$
■ shGPR120$^{f/f}$ (n=6)

***

Sst

Relative mRNA expression

□ non-δ cell
■ GFP-labeled δ cell (n=6)

***

e

9-PAHSA concentration (nM)

□ 2.8mM Glc
■ 11.1mM Glc (n=6)

9-PAHSA

***

f

Fructose Glucose ·····> Acetyl-CoA ·····> C18:0 → C18:1(Oleic acid)

MK8245

(-)

SCD1

Diet ·····> C18:2(Linoleic acid) ·····> VLC-PUFA

FADS2

(-)

SC26196

**Fig.S2: δ cell-specific knockdown of GPR120 in pancreatic islets.**

(a) Plasmid map of pLenti-CAG-DIO-EGFP-mir30shRNA (GPR120) used to package GPR120-shRNA$^{f/f}$ lentivirus.

(b) Schematic of low-leak cre recombinase-mediated EGFP-GPR120shRNA expression. The specific RNA interference sequence of GPR120 we chose in this study was CCGAUUUGCACAUUGGAUUTT (5'-3'). The pLenti-CAG-DIO-EGFP-mir30shRNA (GPR120) plasmid was used to package GPR120-shRNA$^{f/f}$ lentivirus obtained from OBiO Technology Co., Ltd. by which GPR120 shRNA expression prevented functional transcription due to opposite orientation toward the promoter and locked in the forward orientation after both excision and inversion in the presence of Cre recombinase.

(c) Co-immunostaining of somatostatin (RFP) and GPR120 shRNA$^{f/f}$ (GFP)in islets isolated from *Sst-Cre$^{+/-}$* mice. Scale bars, 50μm.

(d) Left panel: GPR120 mRNA level in primary δ cells isolated from *Sst-Cre$^{+/-}$* mice pancreatic islets which infected with lentiviruses expressing a control sequence or GPR120 shRNA$^{f/f}$. Right panel: Sst mRNA level in primary δ cells isolated from *Sst-Cre$^{+/-}$* mice pancreatic islets infected with GPR120 shRNA$^{f/f}$ lentiviruses. Data are from six independent experiments (n=6).

(e) Determination of the 9-PAHSA concentration in 100 μl of supernatant from 200 islets in response to treatment with 2.8 mM or 11.1 mM glucose for 1 h. ***$p<0.001$ for islet supernatants treated with 1 mM glucose compared with those treated with 11.1 mM glucose. The bars represent mean ± SEM. All data statistics were analyzed using one-way ANOVA with Dunnett's post hoc test.

(f) Synthetic pathway of oleic acid and degradative pathway of linoleic acid.

Figure S3

a

Ligand	Assay	pEC50	Emax
TUG891	β-arrestin1	6.52±0.112	0.01±0.001
	β-arrestin2	6.65±0.304	0.01±0.001
	Gi	7.27±0.030	9987±700.043
	Gq	5.53±0.052	0.02±0.001
OA	β-arrestin1	5.48±0.069	0.01±0.001
	β-arrestin2	4.65±0.482	0.01±0.005
	Gi	4.02±0.049	6146.67±93.514
	Gq	4.01±0.188	0.04±0.004
LA	β-arrestin1	5.57±0.097	0.01±0.002
	β-arrestin2	6.22±0.094	0.01±0.001
	Gi	3.75±0.067	7849.33±200.184
	Gq	4.97±0.030	0.04±0.005
PAHSA	β-arrestin1	7.00±0.072	0.01±0.001
	β-arrestin2	6.17±0.324	0.01±0.001
	Gi	3.95±0.052	7884.67±78.624
	Gq	5.27±0.071	0.02±0.001

b
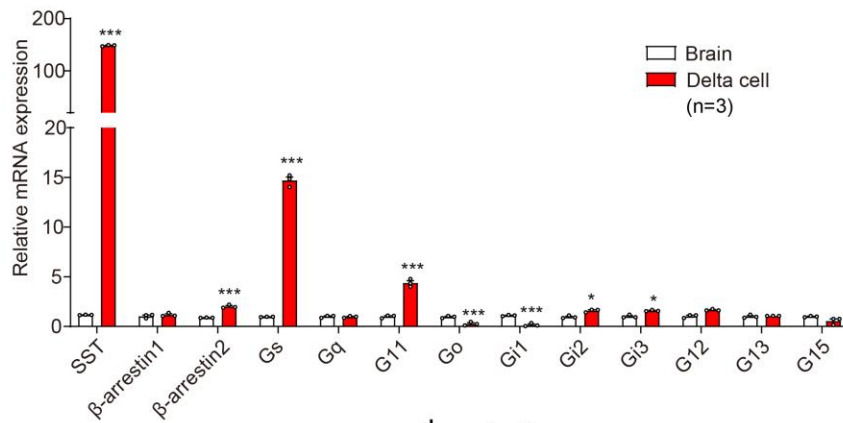
c
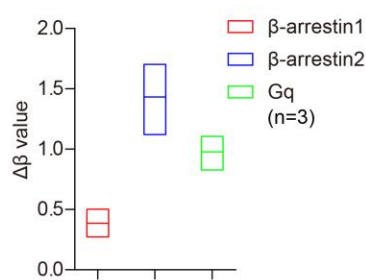
d

e

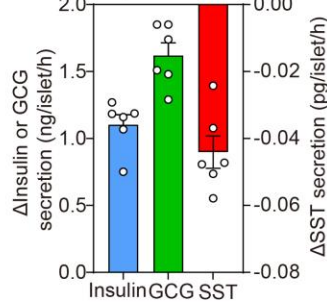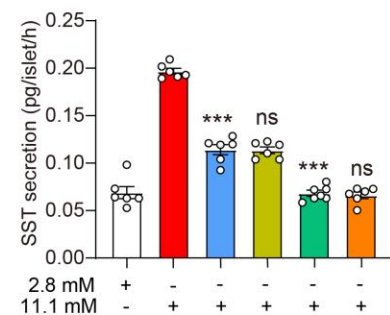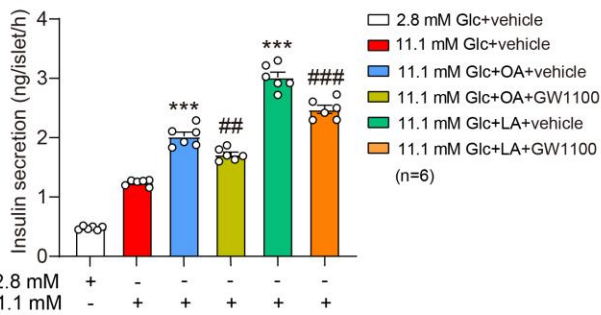## f

Fig.S3: Biases of GPR120 endogenous ligands leading to functional differences

(a) pEC50 and Emax of β-arrestins recruitment, cAMP inhibition and Gβγ release from Gq in GPR120-overexpresing HEK293 cells in response to TUG891, PAHSA, OA and LA. The pEC50 and Emax values are represented as the mean ± SEM of three independent experiments.

(b) qRT-PCR analysis of the mRNA expression levels of several genes, including SST, β-arrestin1, β-arrestin2, Gs, Gq, G11, Go, Gi1, Gi2, Gi3, G12, G13, G15 in brains or δ cells. Primary δ cells were derived from the islets of $Sst^{cre}Rosa^{lsl-GFP}$ mice. The data are from three independent experiments (n=3). *P < 0.05, ***P < 0.001, for δ cells isolated from islets compared with brains.

(c) Difference of the β value between OA and LA stimulated β-arrestins recruitment and heterotrimeric Gq dissociation in GPR120-overexpressing HEK293 cells. Data are from six independent experiments (n=6).

(d) Differences in LA- vs. OA-regulated SST or insulin secretion upon treatment with 11.1 mM glucose. The Δ-values are presented as bar graphs. The data are from six independent experiments (n=6).

(e-f) Effects of OA or LA treatment on glucose-induced SST (e) and insulin (f) secretion in islets isolated from WT mice pretreated with vehicle or 10 μM GPR40 inhibitor GW1100. A total of 300 islets from 4-6 WT mice were grouped (50 islets/group) for SST or insulin secretion experiment. The data are from six independent experiments (n=6). ***p<0.001, for islets treated with OA or LA compared with those treated with vehicle. ##p<0.01, ###p<0.001 and ns, no significant difference, for islets treated with OA or LA pretreated with 10 μM GW1100 compared with those treated with vehicle.

The bars represent mean ± SEM. Data statistics were analyzed using one-way ANOVA with Dunnett's post hoc test.

Figure S4
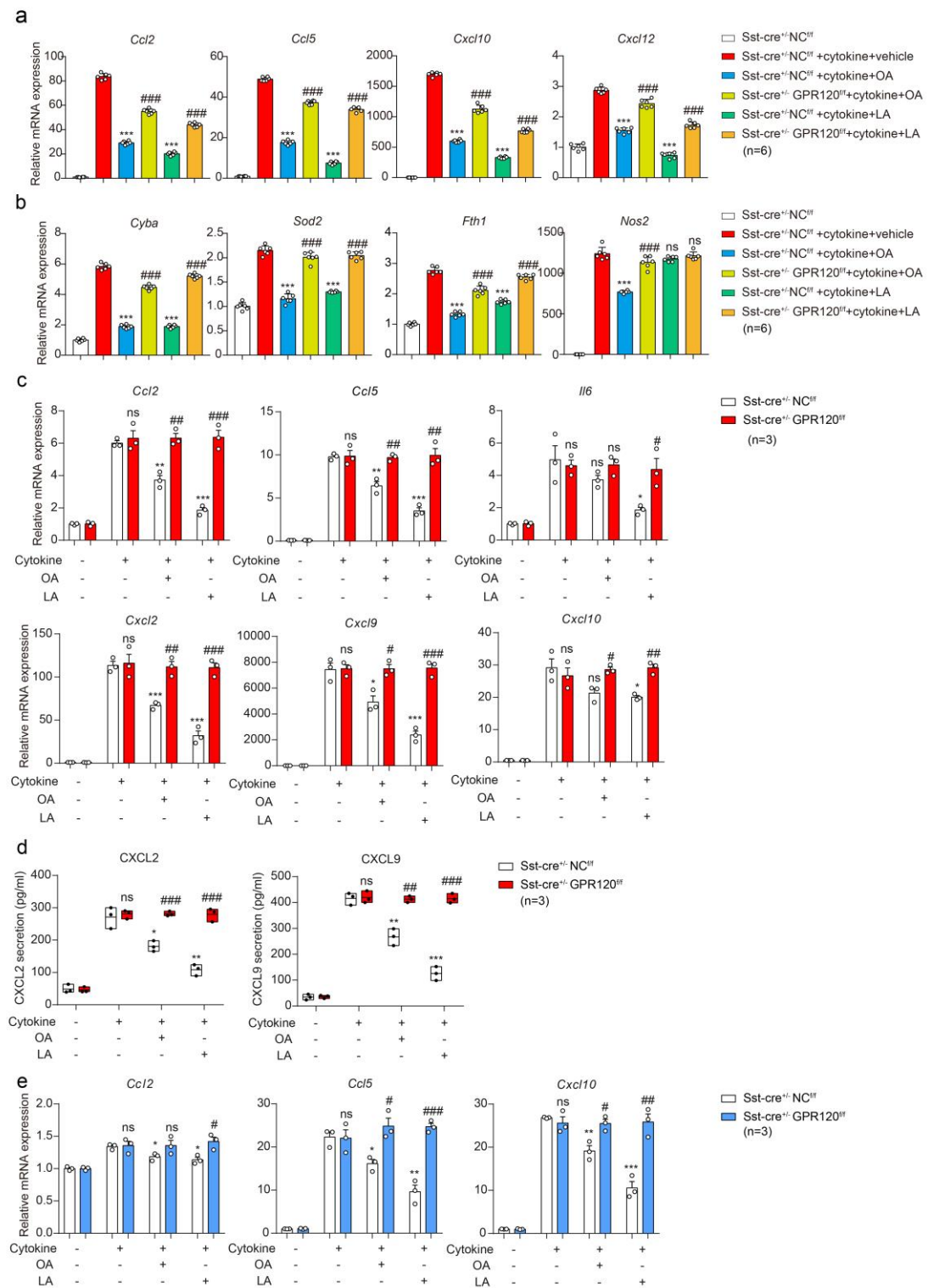
Fig. S4: Effects of GPR120 expressed in pancreatic δ cell to reduce inflammation of pancreatic islets

(a) Effects of OA and LA treatment on the mRNA levels of inflammation markers stimulated by proinflammatory cytokines in islets isolated from *Sst-Cre*^{+/-} mice pretreated with lentiviruses

expressing a control sequence or GPR120 shRNA$^{f/f}$.

(b) Effects of OA and LA treatment on the mRNA levels of stress response genes stimulated by proinflammatory cytokines in islets isolated from *Sst-Cre*$^{+/-}$ mice pretreated with lentiviruses expressing a control sequence or GPR120 shRNA$^{f/f}$.

(c) Effects of 200 μM OA and 200 μM LA treatment on the mRNA level of inflammation marker genes, *Ccl2*, *Ccl5*, *Il6*, *Cxcl2*, *Cxcl9* and *Cxcl10* stimulated by proinflammatory cytokines (30 U/ml IL-1β, 1000 U/ml TNFα, and 1000 U/ml IFNγ) in primary δ cells derived from the islets of *Sst-Cre*$^{+/-}$ mice pretreated with lentiviruses expressing a control sequence or GPR120 shRNA$^{f/f}$. Data are from three independent experiments (n=3).

(d) Effects of 200 μM OA and 200 μM LA treatment on the secretion of inflammation marker proteins, CXCL2 and CXCL9 stimulated by proinflammatory cytokines (30 U/ml IL-1β, 1000 U/ml TNFα, and 1000 U/ml IFNγ) in primary δ cells derived from the islets of *Sst-Cre*$^{+/-}$ mice pretreated with lentiviruses expressing a control sequence or GPR120 shRNA$^{f/f}$. Data are from three independent experiments (n=3).

(e) mRNA levels of *Ccl2*, *Ccl5* and *Cxcl10* in islets isolated from WT mice cultured with the supernatants of primary δ cells derived from the islets of *Sst-Cre*$^{+/-}$ mice pretreated with lentiviruses expressing a control sequence or GPR120 shRNA$^{f/f}$ stimulated by proinflammatory cytokines (30 U/ml IL-1β, 1000 U/ml TNFα, and 1000 U/ml IFNγ) alone or in combination with OA (200 μM) or LA (200 μM). Data are from three independent experiments (n=3).

In a-b, A total of 600 islets from 8-10 *Sst-Cre*$^{+/-}$ mice were grouped (100 islets/group) for RNA extraction. The data are from six independent experiments (n=6). ***p<0.001, and ns, no significant difference, for islets derived from *Sst-Cre*$^{+/-}$ mice treated with OA or LA compared with those treated with vehicle upon stimulation with cytokines; ###p<0.001, and ns, no significant difference, for islets derived from *Sst-Cre*$^{+/-}$ mice treated with lentiviruses expressing GPR120 shRNA compared with those treated with lentiviruses expressing a control sequence upon stimulation with cytokines and OA or LA. In c-e, *P < 0.05, **P < 0.01, ***P < 0.001 and ns, no significant difference, for islets treated with OA or LA compared with islets treated with vehicle; #P < 0.05, ##P < 0.01, ###P < 0.001 and ns, no significant difference, for primary δ cells derived from the islets of *Sst-Cre*$^{+/-}$ mice pretreated with lentiviruses expressing GPR120 shRNA$^{f/f}$ compared with expressing negative control sequence. The bars represent mean ± SEM. All data statistics were analyzed using two-way ANOVA with Dunnett's post hoc test.

Figure S5
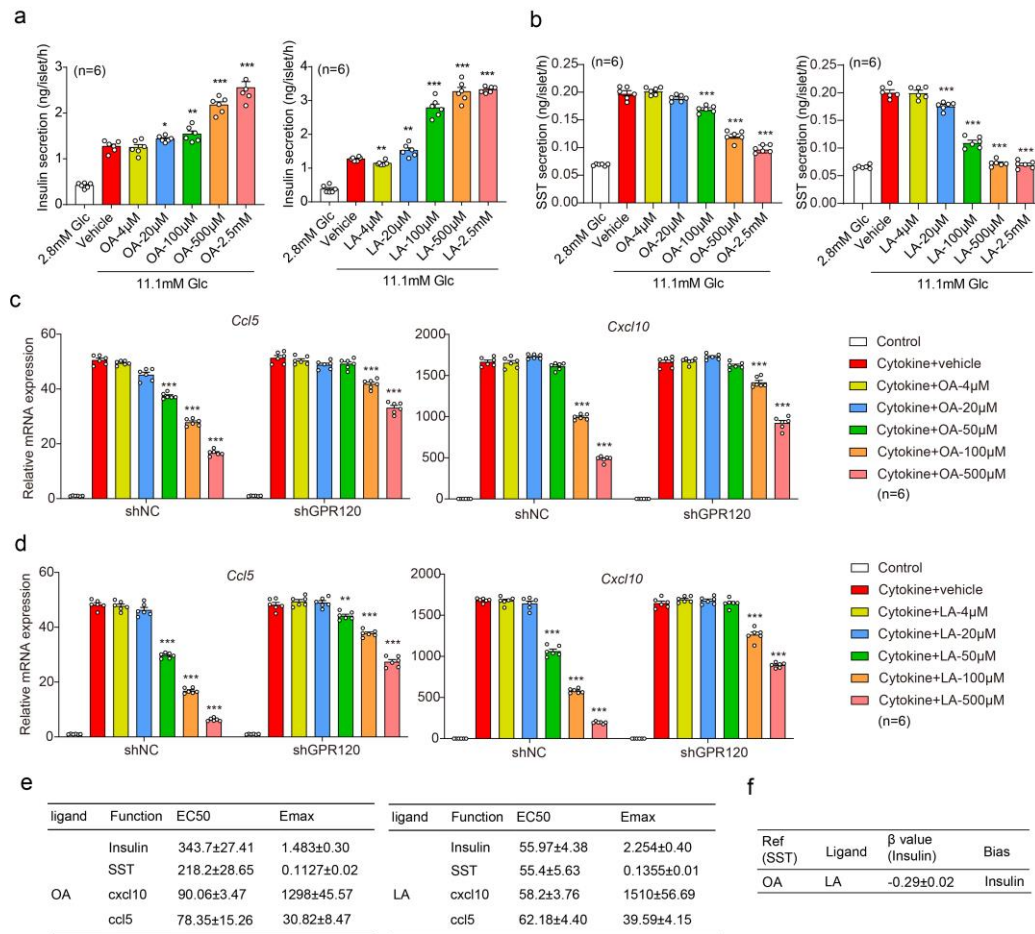
Fig.S5: Concentration-dependent anti-inflammatory of pancreatic islets treated by endogenous ligand (OA and LA) of GPR120

(a-b) Glucose-induced insulin (a) or SST (b) secretion in islets isolated from WT mice upon stimulation with gradient concentration of OA or LA. A total of 350 islets from 6-8 WT mice were grouped (50 islets/group) for insulin or SST secretion experiment. The data are from six independent experiments (n=6).

(c-d) Effects of gradient concentration of OA or LA treatment on the mRNA levels of ccl5 or cxcl10, stimulated by proinflammatory cytokines (30 U/ml IL-1β, 1000 U/ml TNFα, and 1000 U/ml IFNγ) in islets isolated from WT mice pretreated with adenoviruses expressing control or GPR120 shRNA. The data are from six independent experiments (n=6).

(e) EC50 and Emax of promoting insulin secretion and inhibit ccl2 and cxcl10 expression functions of islets isolated from WT mice in response to OA or LA. The EC50 and Emax values are represented as the mean ± SEM of six independent experiments (n=6).

(f) Function bias of LA calculated through operational model using OA ligand as reference.

(a-d) *p＜0.05, **p<0.01, ***p<0.001, for islets isolated from WT mice treated with OA or

LA compared with those treated with vehicle upon the stimulation of cytokine. The bars represent mean ± SEM. All data statistics were analyzed using one-way ANOVA with Dunnett's post hoc test.

Figure S6
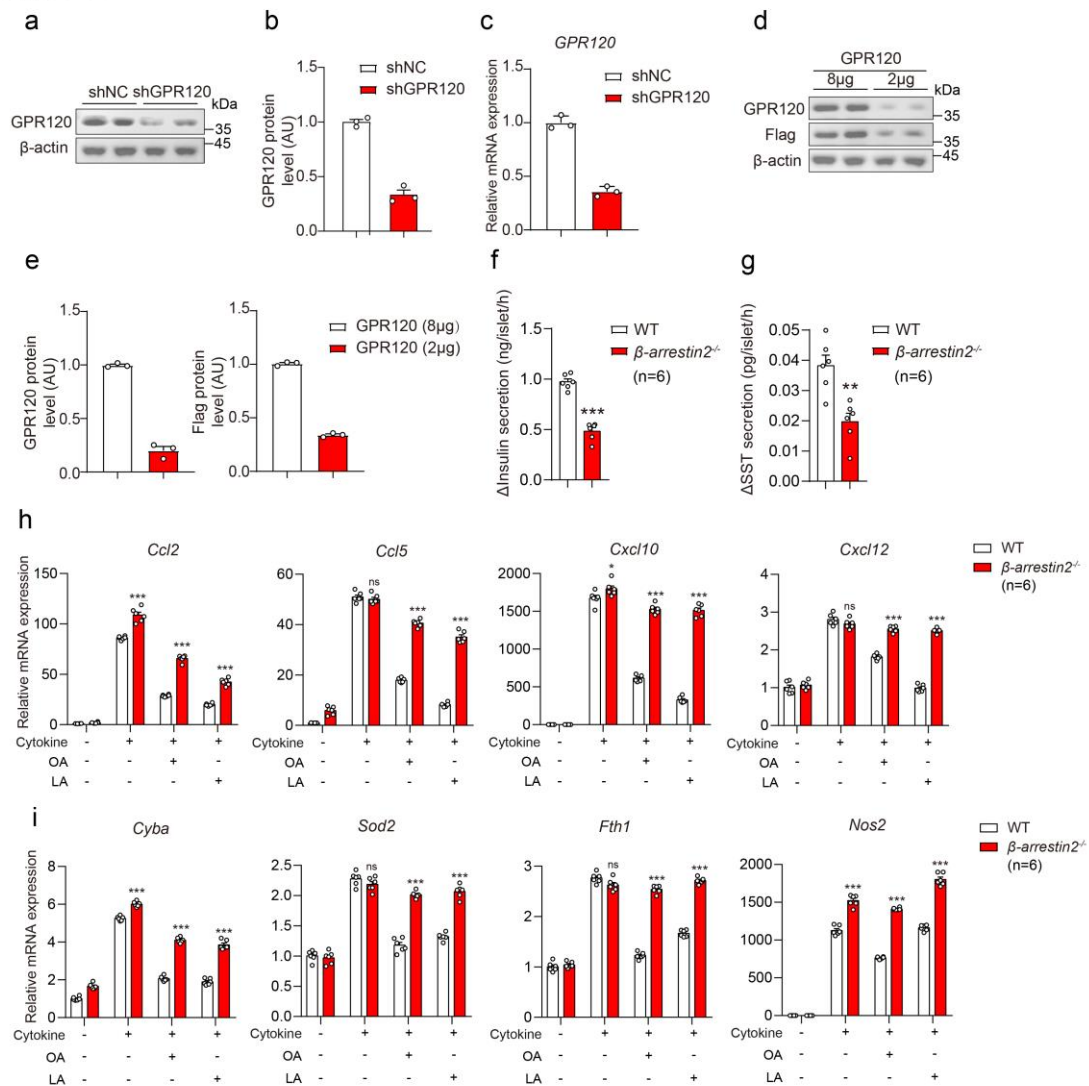
Fig. S6. Contribution of β-arrestin2-mediated biased GPR120 signaling to islet function.

(a) Representative western blots showing the expression of GPR120 and β-actin in pancreatic islets. The anti-GPR120 antibody was used. Islets from WT mice were grouped (400 islets/group) and treated with adenoviruses expressing a control sequence or GPR120 shRNA.

(b) Quantification of GPR120 level relative to β-actin. The data are correlated with Fig. S6a and are from three independent experiments (n=3).

(c) qRT-PCR analysis of the mRNA expression levels of GPR120 in islets isolated from WT mice pretreated with adenoviruses expressing control or GPR120 shRNA. A total of 200 islets from 2-4 WT mice were grouped (100 islets/group) for RNA extraction. The data are from three independent experiments (n=3).

(d) Representative western blots showing the expression of GPR120 in HEK293 cells monitored by anti-Flag or anti-GPR120 antibodies.

(e) Quantification of expression levels of GPR120 using β-actin as controls. The data are correlated with Fig. S6d and are from three independent experiments (n=3).

(f-g) Difference between the effects of LA and OA on glucose-induced insulin(f) or SST (g) secretion in islets isolated from WT and *β-arrestin2*$^{-/-}$ mice. Data are from six independent experiments (n=6).

(h) Effects of OA and LA treatment on the mRNA levels of inflammation markers stimulated by proinflammatory cytokines in islets isolated from *β-arrestin2*$^{-/-}$ mice compared with WT mice.

(i) Effects of OA and LA treatment on the mRNA levels of stress response genes stimulated by proinflammatory cytokines in islets isolated from *β-arrestin2*$^{-/-}$ mice compared with WT mice. In h-i, a total of 400 islets from 6-8 WT or *β-arrestin2*$^{-/-}$ mice were grouped (100 islets/group) for RNA extraction. The data are from six independent experiments (n=6).

(f-g) **$p<0.01$, ***$p<0.001$, for islets isolated from WT mice compared with islets isolated from *β-arrestin2*$^{-/-}$ mice. (h-i) *$p<0.05$, ***$p<0.001$, and ns, no significant difference, for islets isolated from WT mice compared with islets isolated from *β-arrestin2*$^{-/-}$ mice upon treatment with cytokines and OA or LA. The bars represent mean ± SEM. All data statistics were analyzed using one-way (f-g) or two-way (h-i) ANOVA with Dunnett's post hoc test.

Figure S7
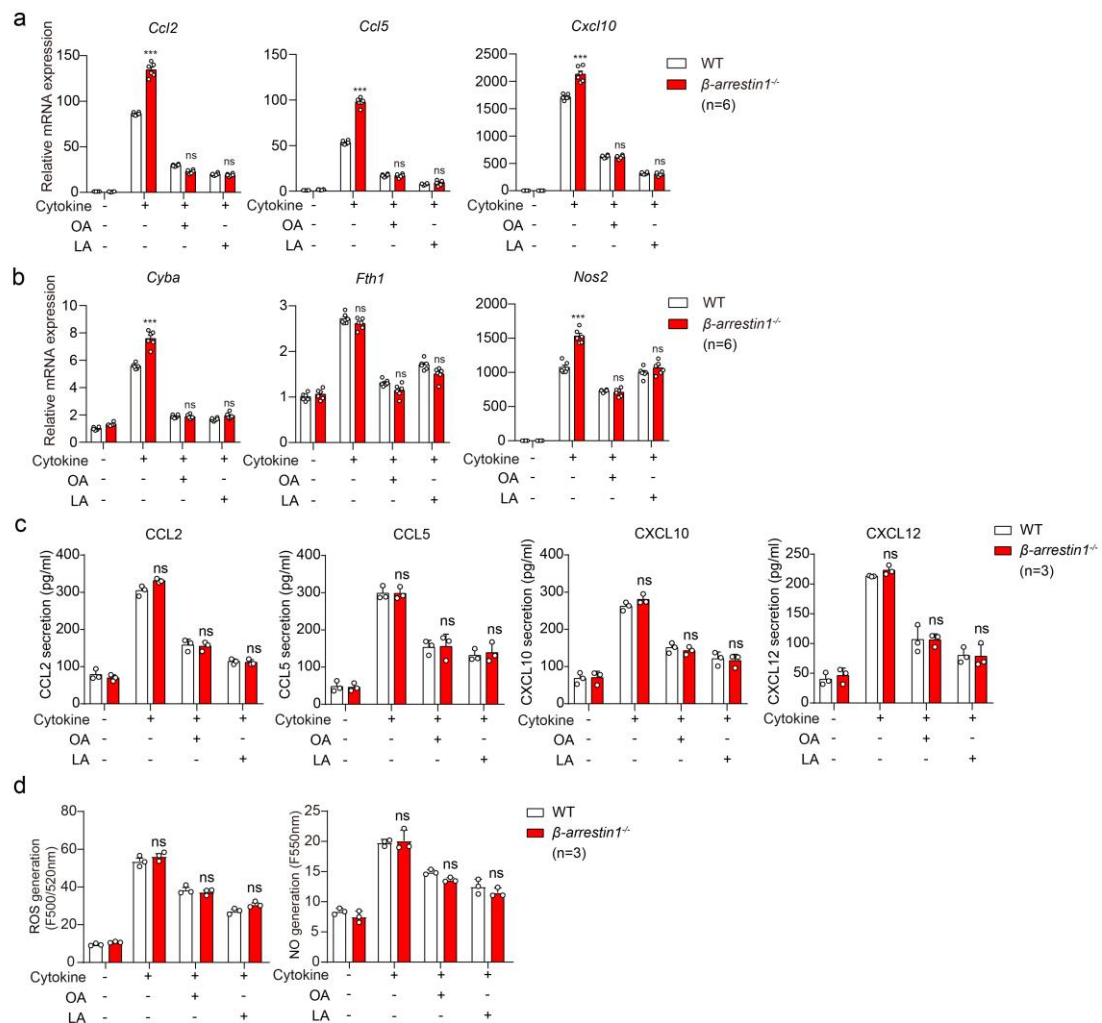
Fig. S7: Contribution of β-arrestin1-mediated biased GPR120 signaling to islet function.

(a) Effects of OA and LA treatment on the mRNA levels of inflammation markers stimulated by proinflammatory cytokines in islets isolated from *β-arrestin1*^{-/-} mice compared with WT mice.

(b) Effects of OA and LA treatment on the mRNA levels of stress response genes stimulated by proinflammatory cytokines in islets isolated from β-arrestin1^{-/-} mice compared with WT mice. In a-b, A total of 400 islets from 6-8 WT or *β-arrestin1*^{-/-} mice were grouped (100 islets/group) for RNA extraction in one experiment. The data are from six independent experiments (n=6).

(c) Effects of OA and LA treatment on the secretion of inflammation marker proteins stimulated by proinflammatory cytokines in islets isolated from *β-arrestin1*^{-/-} mice compared with WT mice. A total of 400 islets from 6-8 WT or *β-arrestin1*^{-/-} mice were grouped (100 islets/group) for secretion experiment. The data are from three independent experiments (n=3).

(d) Effects of OA and LA treatment on the fluorescence levels of ROS and NO in islets isolated

from WT mice or *β-arrestin1*^{-/-} mice. A total of 600 islets from 8-12 WT or *β-arrestin1*^{-/-} mice were grouped (150 islets/group) for ROS and NO experiment in one experiment. The data are from three independent experiments (n=3).
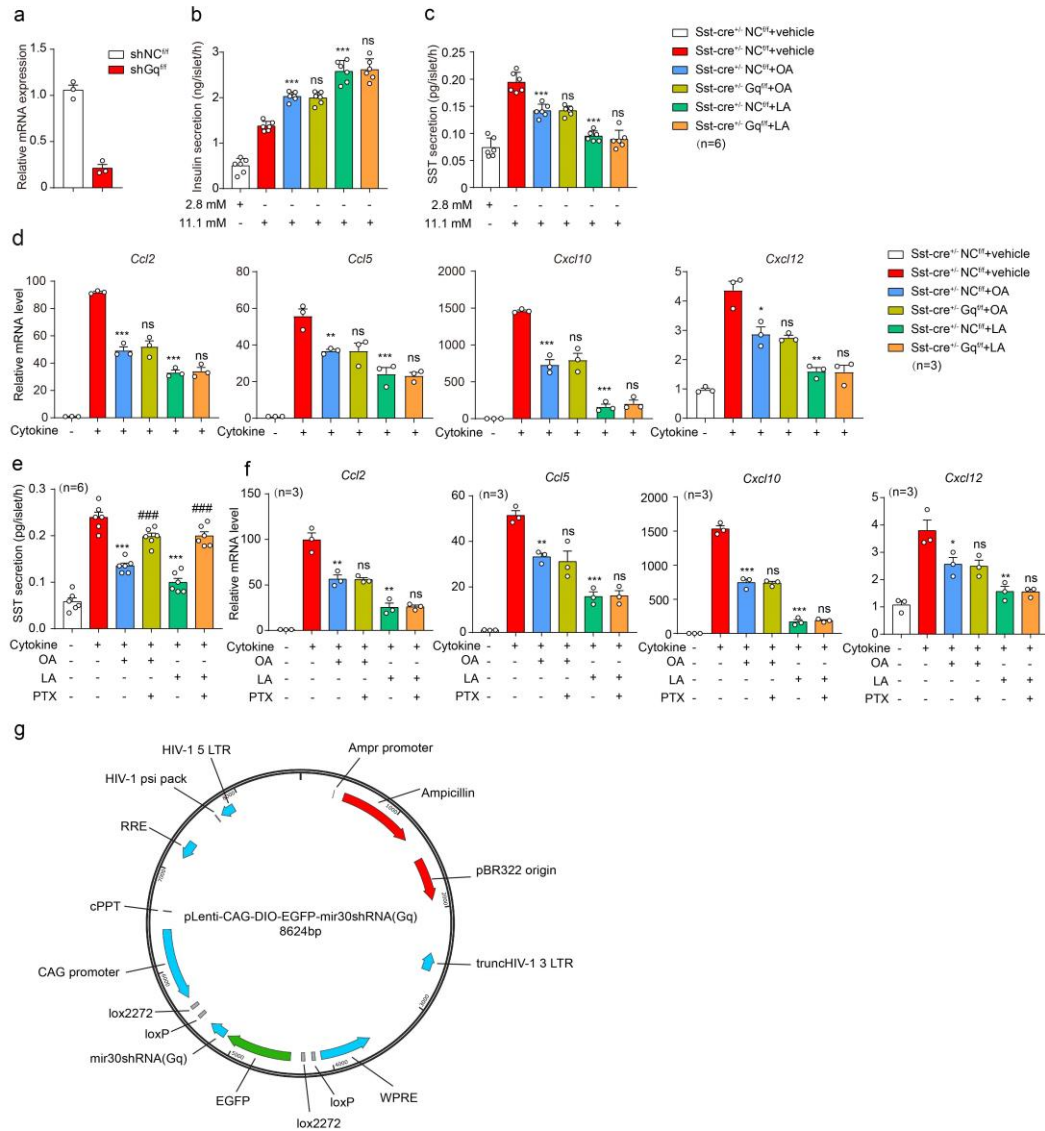
In a-d, ***$p<0.001$, and ns, no significant difference, for islets isolated from WT mice compared with islets isolated from β-arrestin1^{-/-} mice upon treatment with cytokines and OA or LA. The bars and error bars represent the means ± SEMs. All data statistics were analyzed using two-way ANOVA with Dunnett's post hoc test.

Fig.S8: Contribution of Gq/Gi-mediated biased GPR120 signaling to islet function.

(a) Gq mRNA level in primary δ cells isolated from *Sst-Cre*^{+/-} mice pancreatic islets which infected with lentiviruses expressing a control sequence or Gq shRNA[f/f]. Data are from three independent experiments (n=3).

(b-c) Effects of OA or LA treatment on glucose-induced insulin (b) and SST (c) secretion in islets isolated from *Sst-Cre*^{+/-} mice pretreated with lentiviruses expressing a control sequence or GPR120 shRNA[f/f]. A total of 300 islets from 4-6 *Sst-Cre*^{+/-} mice of the indicated genotypes were grouped (50 islets/group) for hormone secretion measurement. The data are from six independent experiments (n=6). Ns, no significant difference, for islets isolated from *Sst-Cre*^{+/-} mice treated with lentiviruses expressing Gq shRNA[f/f] compared with those treated with lentiviruses expressing a control sequence; ***p<0.001 for islets treated with OA or LA compared with those treated with vehicle. The bars represent mean ± SEM. All data statistics

were analyzed using two-way ANOVA with Dunnett's post hoc test.

(d) Effects of 200 μM OA or 200 μM LA treatment on the mRNA level of inflammation marker genes, *Ccl2*, *Ccl5*, *Cxcl10* and *Cxcl12* stimulated by proinflammatory cytokines (30 U/ml IL-1β, 1000 U/ml TNFα, and 1000 U/ml IFNγ) in islets isolated from *Sst-Cre*^{+/-} mice pretreated with lentiviruses expressing a control sequence or GPR120 shRNA[f/f]. Data are from three independent experiments (n=3).

(e) Effects of 200 μM OA or 200 LA treatment on glucose-induced SST secretion in islets isolated from WT mice pretreated with PTX (100 ng/ml) or vehicle for 16h. A total of 300 islets from 6-8 wild type mice of the indicated genotypes were grouped (50 islets/group) for SST secretion measurement. The data are from six independent experiments (n=6).

(f) Effects of 200 μM OA or 200 μM LA treatment on the mRNA level of inflammation marker genes, *Ccl2*, *Ccl5*, *Cxcl10* and *Cxcl12* stimulated by proinflammatory cytokines (30 U/ml IL-1β, 1000 U/ml TNFα, and 1000 U/ml IFNγ) in primary δ cells derived from the islets of WT mice pretreated with PTX (100 ng/ml) or vehicle for 16h. Data are from three independent experiments (n=3).

(g) Plasmid map of pLenti-CAG-DIO-EGFP-mir30shRNA (Gq) used to package Gq-shRNA[f/f] lentivirus obtained from OBiO Technology Co., Ltd. The specific RNA interference sequence of Gq we chose in this study was GCACUCUUUAGAACAAUUAUU (5'-3').

(b-d) ns, no significant difference, for islets isolated from *Sst-Cre*^{+/-} mice treated with lentiviruses expressing Gq shRNA[f/f] compared with those treated with lentiviruses expressing a control sequence; $*P < 0.5$, $**P<0.01$, $***p<0.001$, for islets treated with OA or LA compared with those treated with vehicle. The bars represent mean ± SEM. All data statistics were analyzed using two-way ANOVA with Dunnett's post hoc test. (e-f) $*P < 0.5$, $**P<0.01$, $***P < 0.001$, for islets treated with OA or LA compared with islets treated with vehicle. [###]$P < 0.001$, ns, no significant difference, for islets isolated from WT mice pretreated with PTX compared with vehicle. The bars represent mean ± SEM. Data statistics were analyzed using two-way ANOVA with Dunnett's post hoc test.
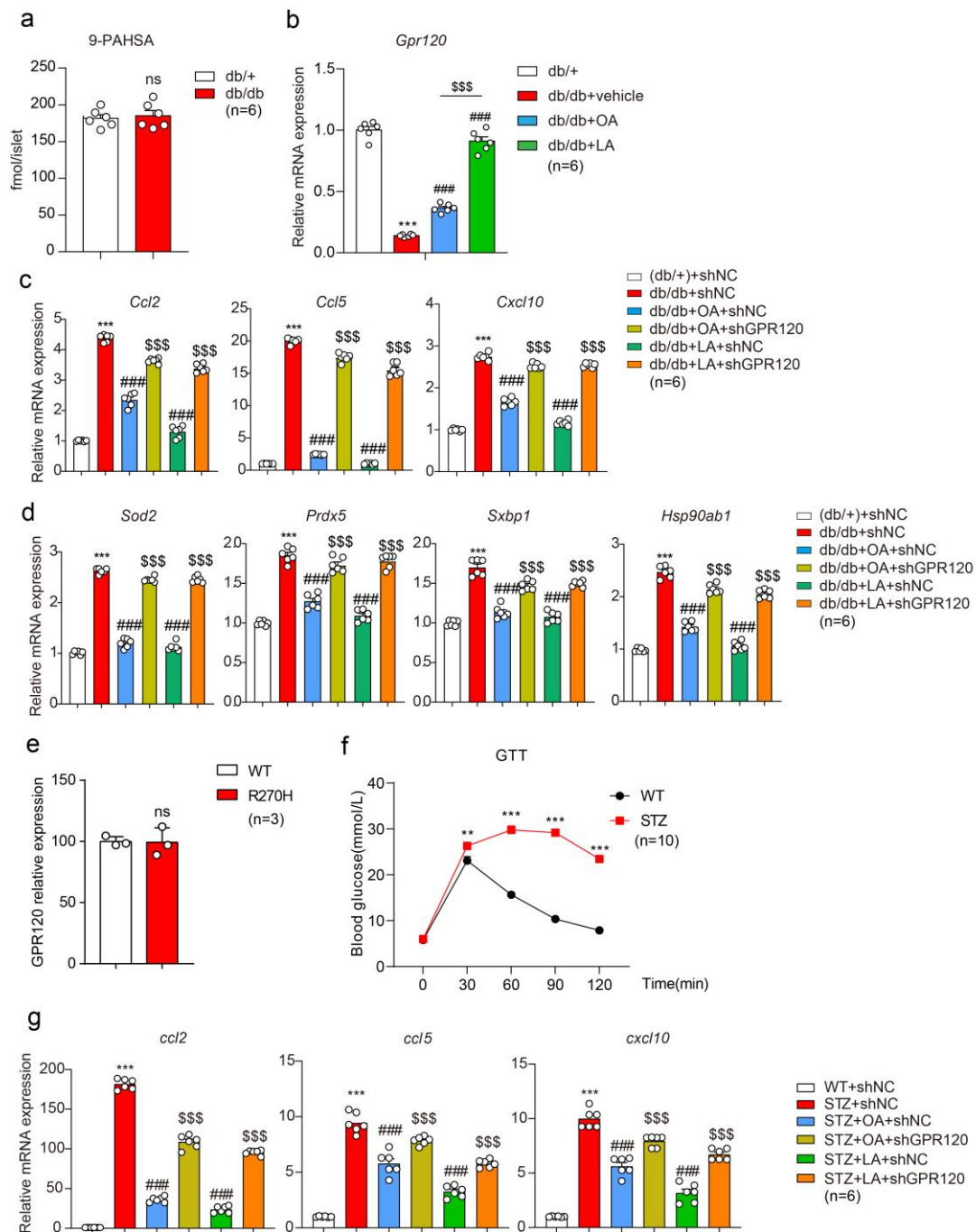
Fig. S9: OA and LA alleviate diabetic phenotypes of db/db and STZ mice.

(a) Contents of PAHSA in islets isolated from db/+ and db/db mice. 1200 islets from 8-10 db/+ or db/db mice were grouped (600 islets/group) for PAHSA content analysis. Data are from six independent experiments (n=6). ns,no significant difference; islets isolated from db/db mice compared with islets isolated from db/+ mice.

(b) Effects of OA and LA treatment on mRNA level of GPR120 in islets isolated from db/+ and db/db mice. 400 islets from 3-5 db/+ or db/db mice were grouped (100 islets/group) for RNA

extraction. Data are from six independent experiments (n=6). ***p<0.001; islets isolated from db/db mice compared with islets isolated from db/+ mice.

(c) Effects of OA and LA treatment on the mRNA levels of inflammation markers stimulated by proinflammatory cytokines in islets isolated from db/+ or db/db mice pretreated with adenoviruses expressing control or GPR120 shRNA.

(d) Effects of OA and LA treatment on the mRNA levels of stress response genes stimulated by proinflammatory cytokines in islets isolated from db/+ or db/db mice pretreated with adenoviruses expressing control or GPR120 shRNA.

(e) Relative expression levels of GPR120 WT and mutant R270H. The expression levels of the R270H were normalized to that of the WT GPR120. Data are from three independent experiments (n=3).

(f) The glucose tolerance test in WT mice and mice treated with STZ (n=10). Overnight fasted animals received intraperitoneally (i.p.) 40 mg/kg (b.w.) streptozotocin (STZ Solarbio Cat. S8050) dissolved in citrate buffer at pH 4.5 in the morning between 9:00 and 10:00 h for 5 consecutive days to obtain the MLD-STZ (multiple low-dose streptozotocin) mice.

(g) Effects of OA and LA treatment on the mRNA levels of inflammation related markers in islets isolated from stz mice compared with islets isolated from control mice.

(a-b) ###p<0.001; islets isolated from db/db mice treated with OA or LA compared with those treated with vehicle. $$$p<0.001; islets isolated from db/db mice treated with OA compared with those treated with LA; (c-d) ***p<0.001 for islets isolated from db/db mice compared with islets isolated from db/+ mice; ###p<0.001 for islets isolated from db/db mice treated with OA or LA compared with those treated with vehicle; $$$p<0.001 for islets isolated from db/db mice pretreated with adenoviruses expressing GPR120 shRNA compared with those treated with OA or LA; (e) Ns, no significant difference, for HEK293 cells transfected with R270H compared with those transfected with wild type GPR120. (f) **p<0.01, ***p<0.001, WT mice treated with STZ compared with these treated with vehicle; (g) **p<0.01, ***p<0.001, and ns, no significant difference; islets isolated from STZ mice treated with OA or LA compared with those treated with vehicle; #p<0.05, ##p<0.01, and ###p<0.001 for islets isolated from STZ mice treated with OA compared with those treated with LA; The bars represent mean ± SEM. Data statistics were analyzed using one-way (a, e) or two-way (b-d and e-g) ANOVA with Dunnett's post hoc test.

Table S1 | List of primers used in the present study

Name	5'-3' sequence
Ccl2-F	GATGCAGTTAACGCCCCACT
Ccl2-R	ACCCATTCCTTCTTGGGGTC
Ccl5-F	ATATGGCTCGGACACCACTC
Ccl5-R	GTGACAAACACGACTGCAAGA
Cxcl10-F	TCCTTGTCCTCCCTAGCTCA
Cxcl10-R	ATAACCCCTTGGGAAGATGG
Cxcl12-F	GACAAGTGTGCATTGACCCG
Cxcl12-R	AGAGGGAGGAGCGAGTTACA
Cyba-F	TGTGTGAAACGTCCAGCAGT
Cyba-R	GTCATGGGGCAGATCGAGT
Sod2-F	AGACACGGCTGTCAGCTTCT
Sod2-R	CTGGACAAACCTGAGCCCTA
Fth1-F	GGCAAAGTTCTTCAGAGCCA
Fth1-R	CATCAACCGCCAGATCAAC
Nos2-F	CAGCTGGGCTGTACAAACCTT
Nos2-R	CATTGGAAGTGAAGCGTTTCG
Prdx5-F	GTTCACCTTCTTTCCCGGTT
Prdx5-R	AGAAGCAGGTTGGGAGTGTG
Sxbp1-F	GAGTCCGCAGCAGGTGC
Sxbp1-R	CAAAAGGATATCAGACTCAGAATCTGAA
Hsp90ab1-F	ACCAGAGGAGAGCAGAGCAG
Hsp90ab1-R	AAGGCTGAGGCAGACAAAAA
Gcg-F	GGCACATTCACCAGCGACTA
Gcg-R	GAGAAGGAGCCATCAGCGTG
Ins2-F	GCTATCCTCAACCCAGCCTAT
Ins2-R	CTCCAGTGCCAAGGTCTGAA
Sst-F	CCACCGGGAAACAGGAACTG
Sst-R	TTGCTGGGTTCGAGTTGGC
lq-1084-INS	GCGGTCTGGCAGTAAAAACTATC
lq-1085-INS	GTGAAACAGCATTGCTGTCACTT
lq-7338-INS	CTAGGCCACAGAATTGAAAGATCT
lq-7339-INS	GTAGGTGGAAATTCTAGCATCATCC

SS-cre-11224	GGGCCAGGAGTTAAGGAAGA
SS-cre-11225	TCTGAAAGACTTGCGTTTGG
SS-cre-9989	TGGTTTGTCCAAACTCATCAA
GFP-oIMR7318	CTCTGCTGCCTCCTGGCTTCT
GFP-oIMR7319	CGAGGCGGATCACAAGCAATA
GFP-oIMR7320	TCAATGGGCGGGGGTCGTT
Gcg-MF	CATGGCATTGGAGCCATAAG
Gcg-MR:	TGTTGGATGGTCTTCACAGCC
Gcg-WR:	CTGGGGTTCTCCTCTGTGTC
GPR120-F	TGCCCCTCTGCATCTTGTTC
GPR120-R	TTTCTCCTATGCGGTTGGGC
GPR40-F	GCTTTCCATTGAACTTGTTAGCC
GPR40-R	CGCTGAGAGCAGCTAGGAAG
GPR41-F	CTTCTTTCTTGGCAATTACTGGC
GPR41-R	CCGAAATGGTCAGGTTTAGCAA
GPR43-F	CTTGATCCTCACGGCCTACAT
GPR43-R	CCAGGGTCAGATTAAGCAGGAG
GPR84-F	CTCCTGCTACCATGAGTCTGT
GPR84-R	GTGCAGTAGAGTAGATCAGCCA
GPR119-F	CTTGCTGTCCTAACCATCCTCA
GPR119-R	CCACGCCAATCAAGGTATCAG

Table S2 | List of antibodies used in the present study

Antibodies	Company	Catalog Number
anti-insulin	Thermo Fisher Scientific	53-9769-82
anti-somatostatin	Abcam	ab30788
anti-glucagon	Millipore	AB932
goat anti-rabbit	Invitrogen	A27034
goat anti-rat	Abcam	ab150157
anti-GFP	Santa Cruz	sc-9996
anti-GPR120	Santa Cruz	sc-390752
anti-β-arrestin-1	Abcam	ab32099
anti-β-arrestin-2	Abcam	ab31294
anti-flag	Sigma-Aldrich	F1804