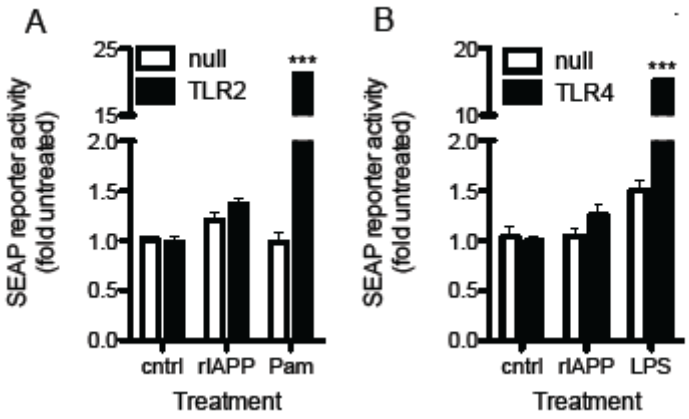
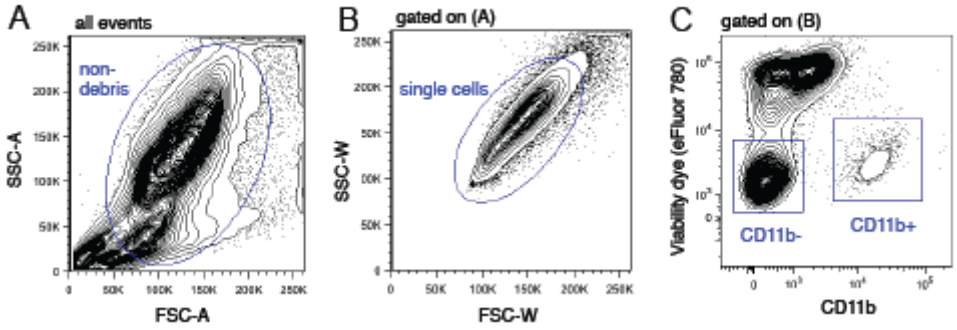
SUPPLEMENTARY DATA

Supplementary Figure 1. Synthetic rodent IAPP does not contain contaminating TLR2 or TLR4 ligands**.** HEK 293 cells cotransfected with (A) human TLR2 or (B) human TLR4 and an NF-κB/AP-1 reporter construct driving SEAP expression were treated with vehicle (cntrl), rIAPP (10 μM), theTLR1/2 ligand Pam3CSK4 (Pam, 10 ng/ml) or the TLR4 ligand LPS (10 ng/ml) for 24 h. SEAP activity was determined by colorimetric assay. ***p<0.001 vs. non-TLR-expressing (null)reporter cell line.

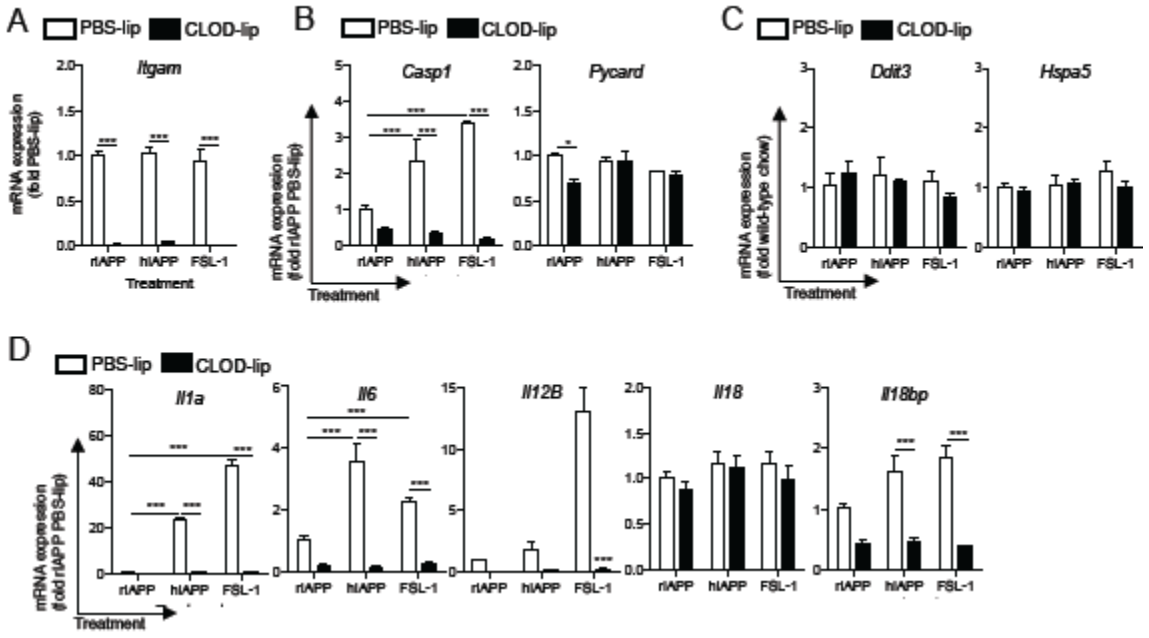


Supplementary Figure 2. Gating strategy for flow cytometric analysis of islet macrophages. Islets were dispersed and analyzed by flow cytometry. (A) Events were gated to exclude debris. (B)Events were gated to exclude doublets. (C) Single cells were gated for analysis of viableCD11b+ and CD11b-islet cells.

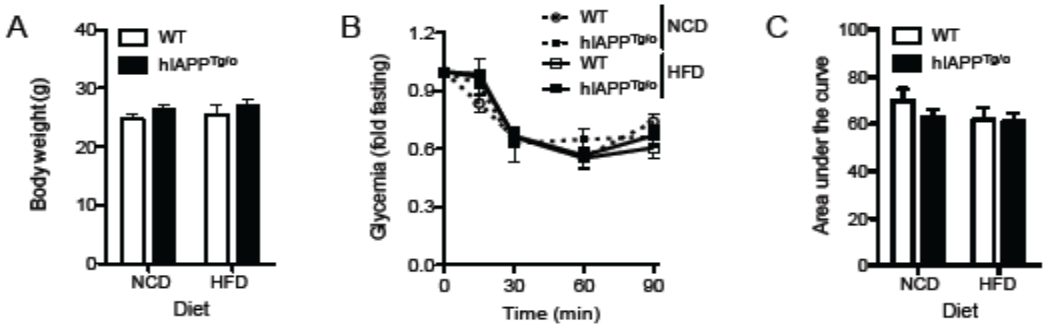


SUPPLEMENTARY DATA

Supplementary Figure 3. Additional gene expression analysis of IAPP-treated islets**.** Islets were isolated from12-wk-old C57BL/6 mice and immediately treated with clodronate-containing liposomes (CLODlip,1 mg/ml clodronate) or control liposomes (PBS-lip) for 36 h, then washed and allowed to recover for 6 h prior to incubation with human IAPP (hIAPP, 10 μM) or the TLR2 ligand FSL-1 (10 ng/ml) for 4 h. mRNA expression of (A) CD11c, (B) inflammasome-related genes, (C) ER stress markers, and (D) cytokines was assessed by RT-qPCR and expression levels were normalized to the housekeeping gene *Rplp0.* Data represent mean ± SEM of islets from 4 mice and are representative of 3 independent experiments. *p<0.05, **p<0.01, *** p<0.001.

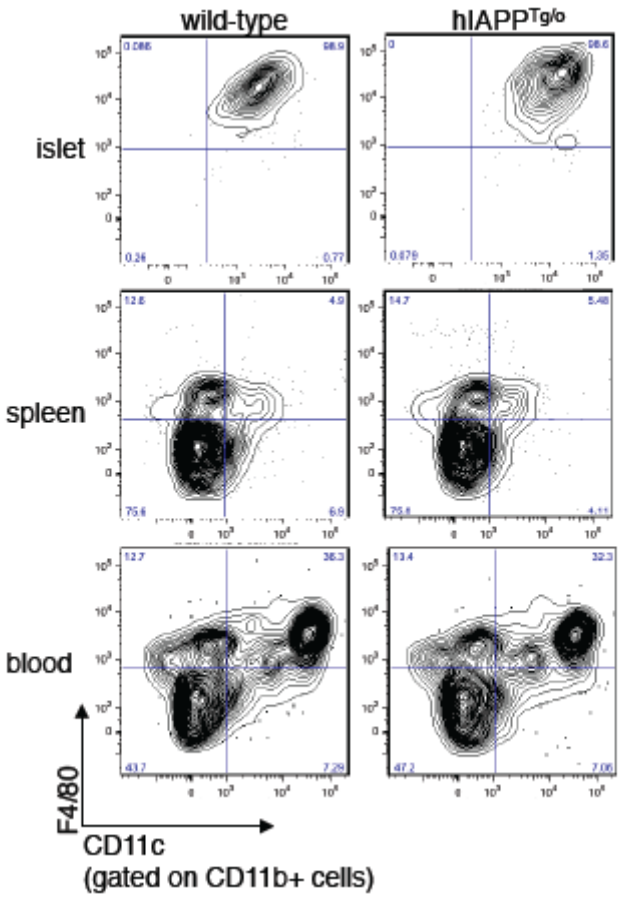


Supplementary Figure 4. FVB mice are resistant to weight gain and insulin resistance with high fat feeding. Female hIAPP transgenic FVB mice (hIAPPTg/o) and wild-type littermate controls (WT) were placed on normal chow (NCD, 13% kcal from fat) or high fat diet (HFD, 45% kcal from fat) for 14 weeks starting at 10 weeks of age. (A) Body weight was assessed at 24 weeks of age. (B) Insulin sensitivity was evaluated by i.p. injection of 1 U/kg insulin and (C) evaluation area under the glycemia curve up to 60 min. Data represent mean ± SEM of 9-14 mice per group.



SUPPLEMENTARY DATA

Supplementary Figure 5. Beta cell hIAPP expression increases CD11c expression in CD11b+F4/80+ cells fromislets but not peripheral blood or spleen. Female hIAPP transgenic FVB mice (hIAPPTg/o) were placed on high fat diet for 14 weeks. Dispersed islets, splenocytes, and peripheral blood leukocytes were analyzed for F4/80 and CD11c expression within the CD11b+ population. Flow cytometry plots are representative of 4-6 mice per group in each of three independent experiments



SUPPLEMENTARY DATA

Supplementary Figure 6. Treatment of hIAPP transgenic islets with clodronate liposomes *ex vivo* improvesinsulin secretion. Islets were isolated from 10-wk-old wild-type or hIAPP transgenic FVB mice (hIAPPTg/o) and immediately treated with CLOD-lip (1 mg/ml clodronate) or PBS-lip for 36 h. Islets were washed and allowed to recover for 6 h prior to culture in RPMI containing 16.7 mM glucose for 5 days to promote amyloid formation. (A) Insulin content and (B) glucose-induced insulin secretion were determined by ELISA.