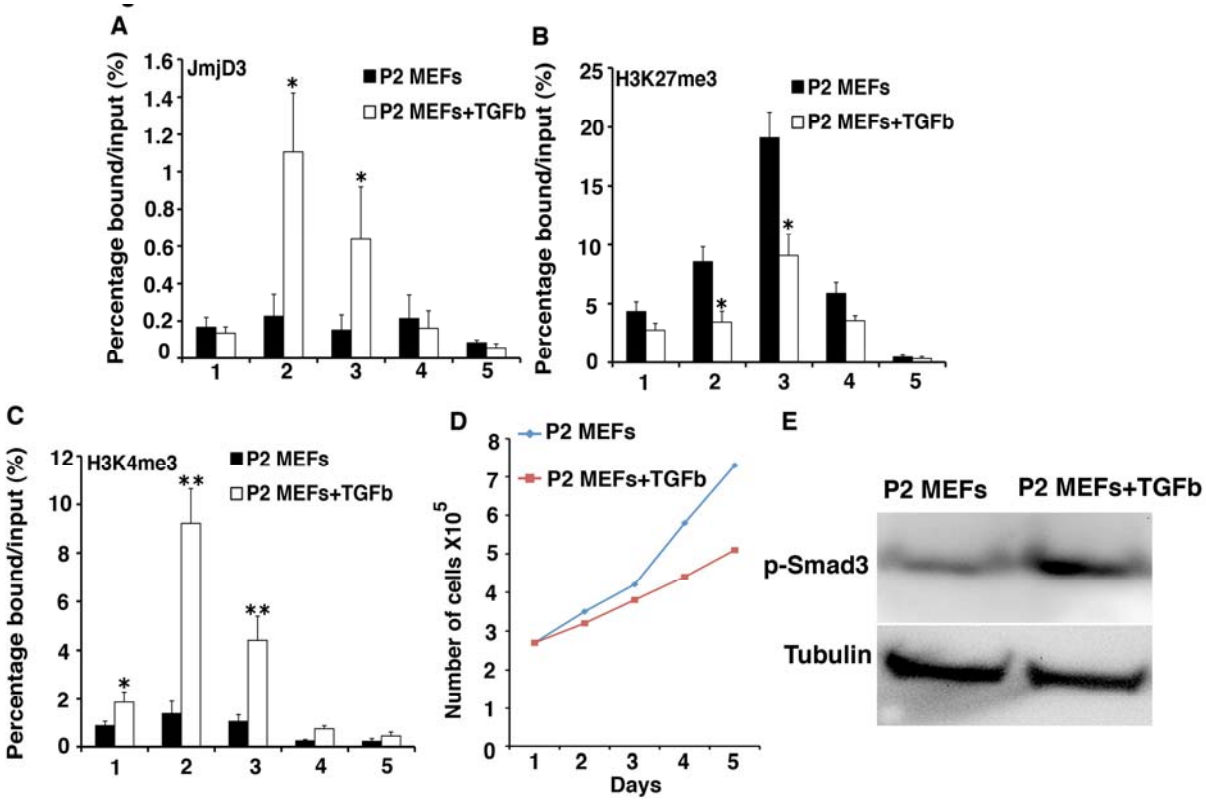
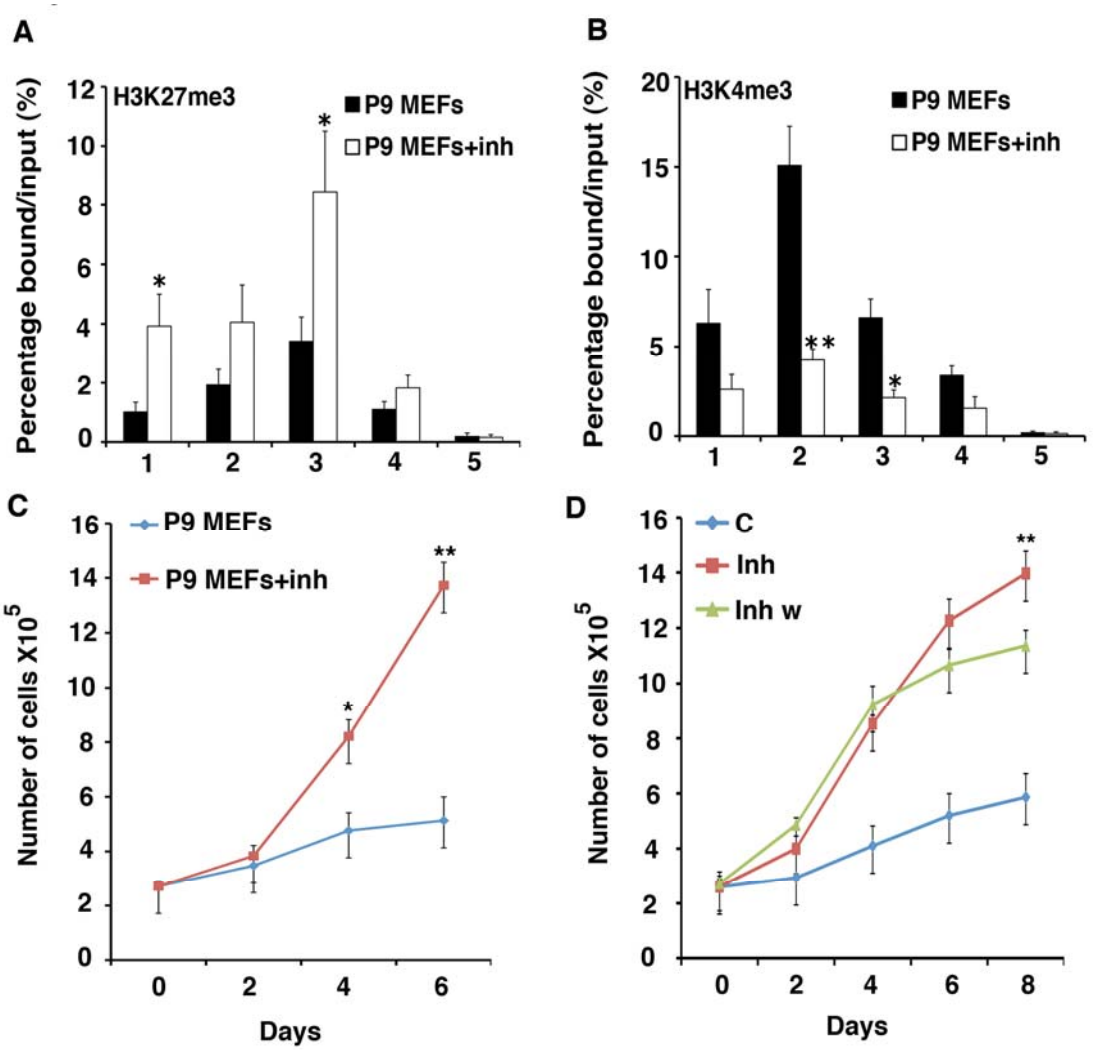
SUPPLEMENTARY DATA

Supplementary Figure S1. (*A*, *B*, *C*) ChIP analyses comparing the recruitment of JmjD3 (A) and levels of H3K27me3 (B) and H3K4me3 (c) at the *Ink4a/Arf* locus, in early passage (P2) MEFs treated with TGF-beta (TGFb), or vehicle control. 1-5 indicate the amplified regions, 5 being negative control. (*D*) Cell doubling in P2 MEFs upon treatment with TGF-beta (TGFb), or vehicle control. (*E*) Western-blotting for p-Smad3 and beta-tubulin in extracts from islets from 9 months old mice, treated with TGF-beta inhibitor, or vehicle control. Representative experiment from (n=3). Error bars indicate ± s.e.m.; *P*-values were determined by unpaired Student's *t*-test. The analyses show a representative from at least three independent experiments. *p < 0.05; ** p<0.01



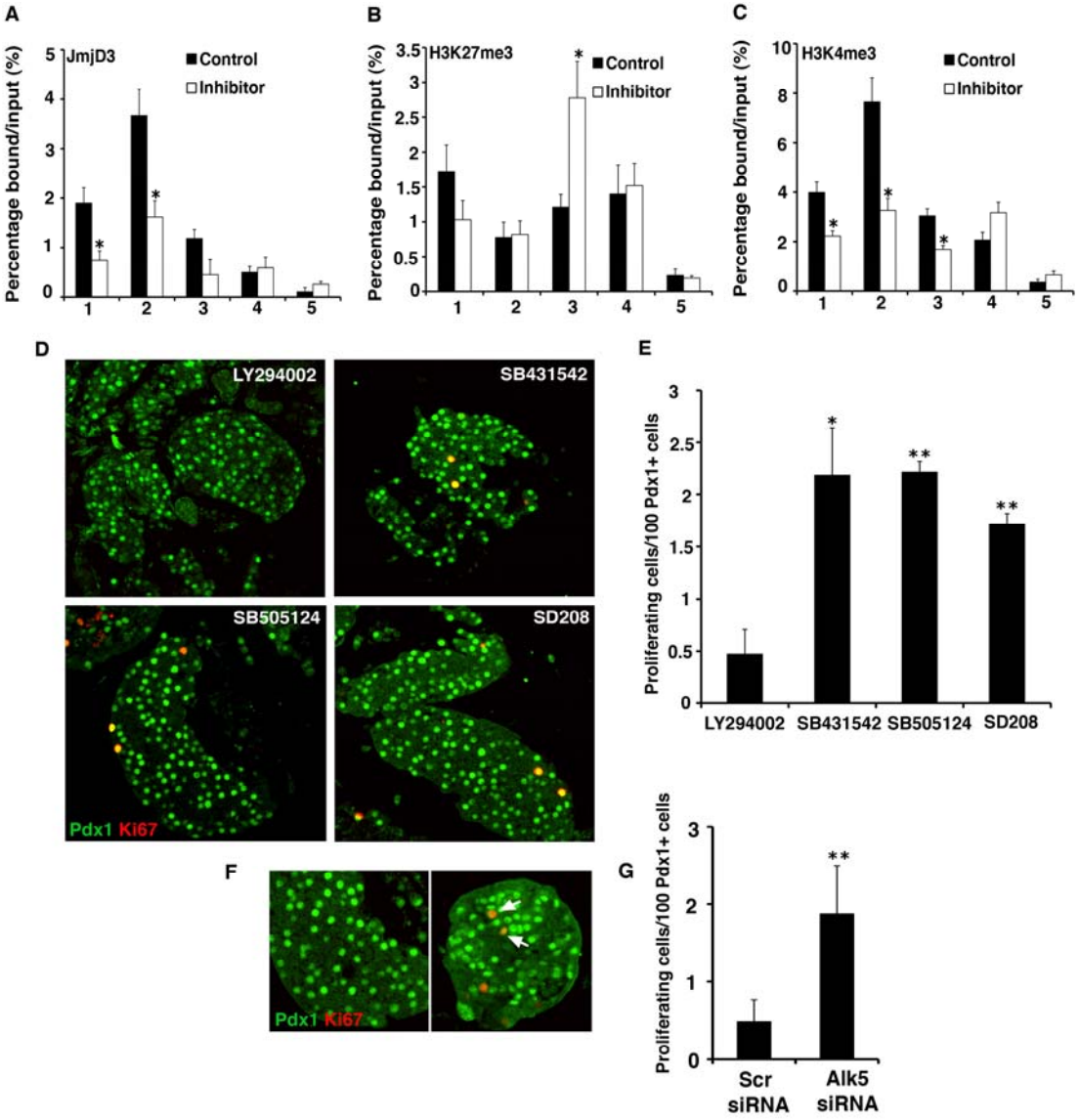
SUPPLEMENTARY DATA

Supplementary Figure S2. (*A*, *B*) ChIP analyses comparing the levels of H3K27me3 (A) and H3K4me3 (B) at the *Ink4a/Arf* locus, in late passage (P9) MEFs treated with TGF-beta inhibitor (inh), or vehicle control. 1-5 indicate the amplified regions, 5 being negative control. (*C*) Cell doubling in P9 MEFs upon treatment with TGF-beta inhibitor (Inh), or vehicle control (N=1). (*D*) Cell doubling in P9 MEFs upon continuous treatment with TGF-beta (Inh), or after inhibitor withdrawl after day 4 (Inh w), or vehicle control (C) (N=1). Error bars indicate ± s.e.m.; *P*-values were determined by unpaired Student's *t*-test. **p* < 0.05; ** *p*<0.01 The analyses show a representative from at least three independent experiments, unless otherwise indicated.



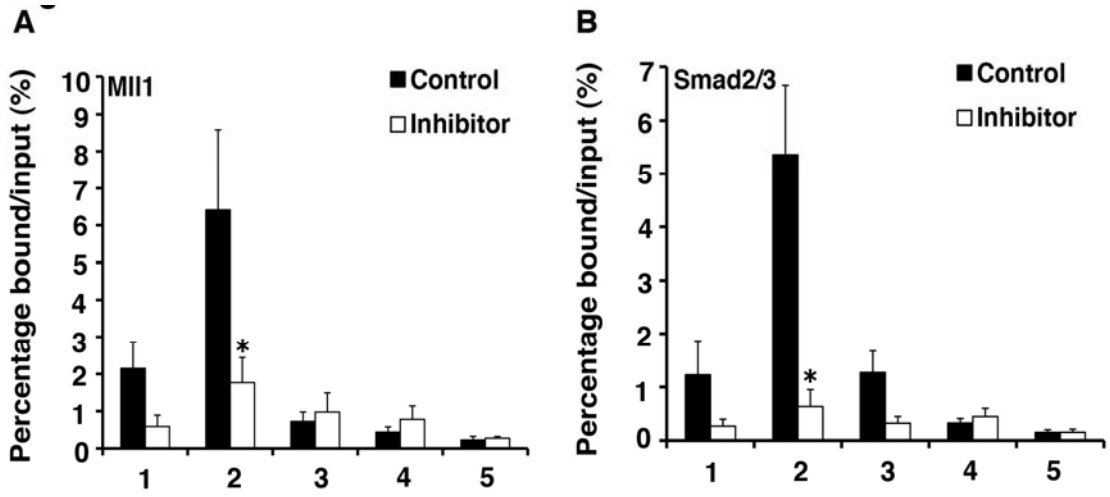
SUPPLEMENTARY DATA

Supplementary Figure S3. (*A*, *B*, *C*) ChIP analyses comparing the recruitment of JmjD3 (A) and levels of H3K27me3 (B) and H3K4me3 (C) at the *Ink4a/Arf* locus, in islets from old (9 months) mice, treated with TGF-beta inhibitor, or vehicle control. 1-5 indicate the amplified regions, 5 being negative control. (*D*, *E*) Immunohistochemistry (D), and quantification (E) for proliferation of beta cells in islets from 9 months old mice, treated with indicated TGF-beta inhibitors (SB431542, SB505124, SD208, or a control small molecule LY294002, using immunostaining with Ki67 antibody (red), and beta cell marker Pdx1 (green). (*F*, *G*) Immunohistochemistry (F), and quantification (G) for proliferation of beta cells in islets from 9 months old mice, treated with *Alk5* siRNA, or control, scrambled siRNA, using immunostaining with ki67 antibody (red), and beta cell marer Pdx1 (green). Error bars indicate ± s.e.m.; *P*-values were determined by unpaired Student's *t*-test. *$p < 0.05$; ** $p<0.01$. The analyses show a representative from at least three independent experiments (N=3), unless otherwise indicated.



SUPPLEMENTARY DATA

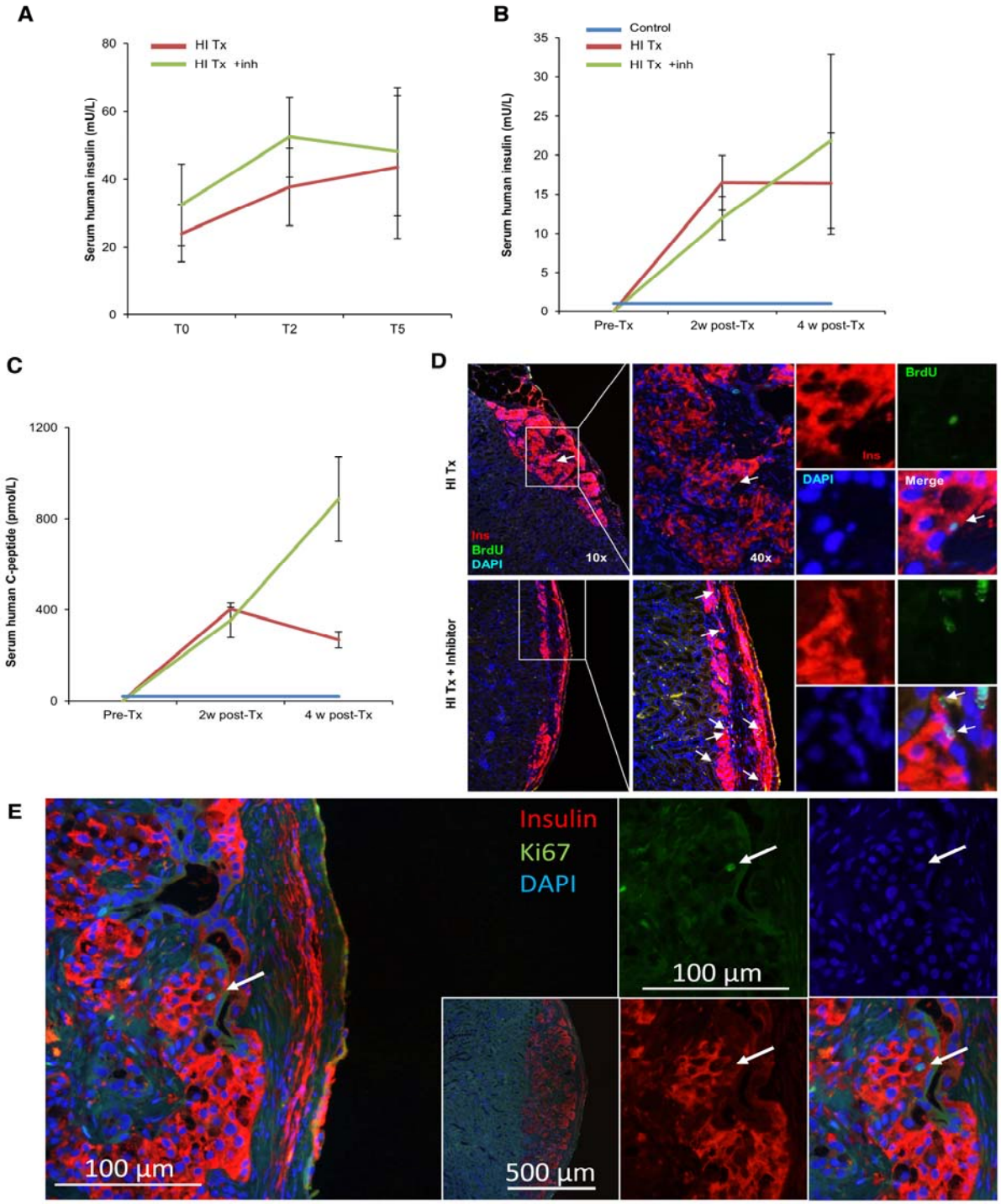
Supplementary Figure S4. (*A*, *B*) ChIP analyses comparing the recruitment of Mll1 (A) and Smad3 (B) at the *Ink4a/Arf* locus, in human islets from adult cadaveric donors, treated with TGF-beta inhibitor, or vehicle control. 1-5 indicate the amplified regions, 5 being negative control. Error bars indicate ± s.e.m.; *P*-values were determined by unpaired Student's *t*-test. $*p < 0.05$. The analyses show a representative from at least three independent experiments (N=3), unless otherwise indicated.



SUPPLEMENTARY DATA

Supplementary Figure S5. (*A*) Acute (first)-phase human insulin secretion (following an intraperitoneal injection of glucose, 3g/Kg body weight) from human islets grafted under the kidney capsule of NSG mice, treated with or without TGF-beta inhibitor. Data are expressed as increase in human insulin at 2 (T2) and 5 (T5) minutes, relative to time 0 (T0). (*B*, *C*) Serum Human insulin (B) and human C-peptide (C) levels. To visualize control group (sham operated mice) in the human insulin and C-peptide graphs we used representative values. Representative experiments from (n=4). Error bars indicate ± s.e.m. *P*-values were determined by unpaired Student's *t*-test. $*p < 0.05$. (*D*) Immunohistochemistry of human islet transplanted (top panels) and human islet transplanted and treated with TGF-beta inhibitor (bottom panels), kidney sections stained with BrdU antibody (green), insulin (red) and DAPI (blue). Arrows mark replicating beta cells. Magnified images show each immunoflourescent staining separately (indicating nuclear gap for replicating beta cell surrounded by insulin) for the proliferating beta-cells. 10x and 40X magnification. Representative experiment from (n=4). (*E*) Immunohistochemistry of human islet transplanted and treated with TGF-beta inhibitor (bottom panels), kidney sections stained with Ki67 antibody (green), insulin (red) and DAPI (blue). Arrows mark replicating beta cells. Magnified images show each immunoflourescent staining separately (indicating nuclear gap for replicating beta cell surrounded by insulin) for the proliferating beta-cells.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Figure S6. (*A*) TUNEL staining (left panels), and quantification (right panel, graph) of paraffin-embedded sections of pancreatic tissue obtained from mice receiving twice/week TGF beta inhibitor treatment for 3 weeks 7 days after human islet transplantation. Scale bar 200 µm. Arrows indicate TUNEL$^+$ beta cells undergoing apoptosis. Inset shows a magnified representative image of TUNEL$^+$ beta cell. (*B*) Morphometric analysis (left panels), and quantification (right panel, graph) of beta cell area of pancreatic sections from DMSO and TGF-beta inhibitor treated mice. (*C*) Representative pancreas sections (magnification x20; left panels) showing insulin (red) positive islets. Nuclear staining by DAPI is shown in blue. The right panel (graph) shows total beta cells per mm^2 pancreatic area. *n*=4 mice each group and ***P<0.05* (student *t*-test). Data are expressed as mean± SEM.