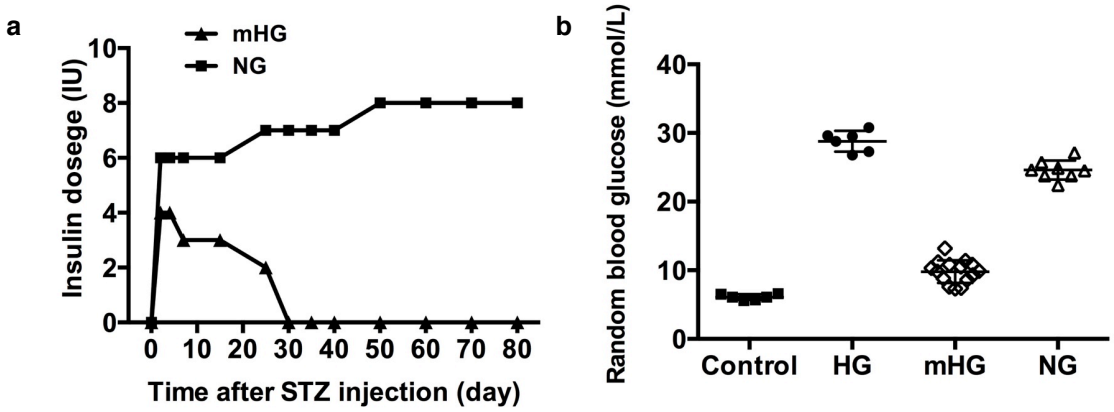
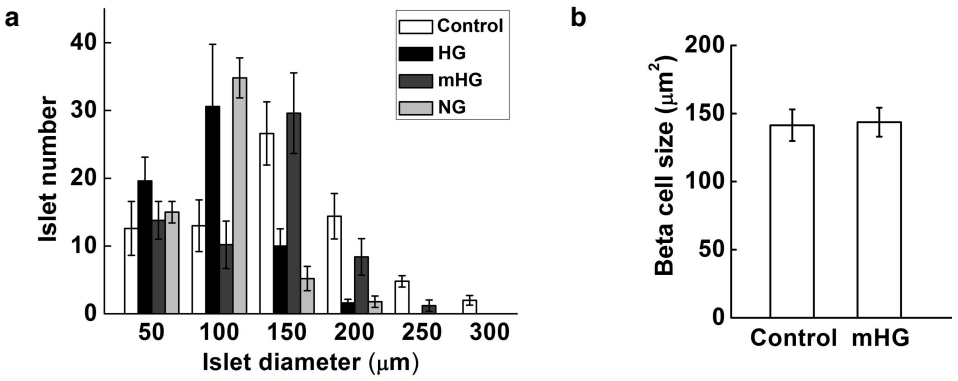
Supplementary Tab.1. List of sequences of forward and reverse primers

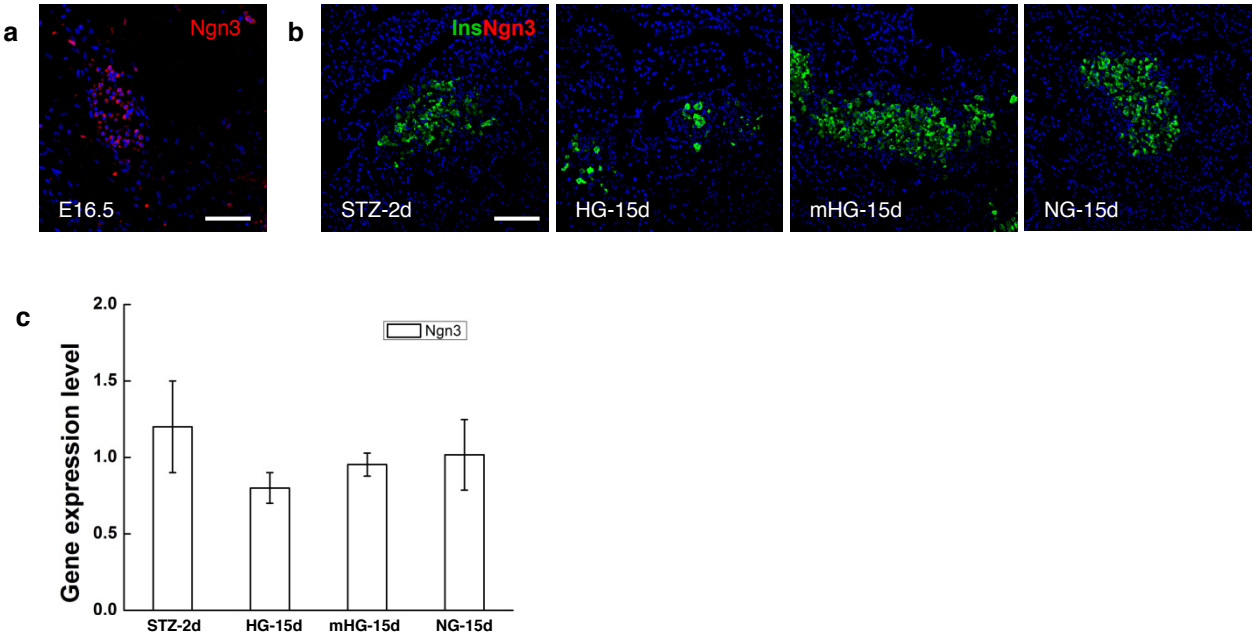
Genes	Primer Sequences	Product size (bp)
Ins1	Forward: 5'-> 3'ggaacgtggtttcttctacac Reverse: 5'-> 3'gggagtggtggactcag	216
Ins2	Forward: 5'-> 3'tcttctacacacccatgtccc Reverse: 5'-> 3'ggtgcagcactgatccac	149
Pdx1	Forward: 5'-> 3'gacacatcaaaatctggttccaaa Reverse: 5'->3'tcccgctactacgtttcttatcttc	75
MafA	Forward: 5'-> 3'cttcagcaaggaggaggtcatc Reverse: 5'-> 3'gcgtagccgcggttctt	67
Nkx6.1	Forward: 5'-> 3'tcttctggcctggggtgatg Reverse: 5'-> 3'ggctgcgtgcttctttctcca	121
Glut2	Forward: 5'-> 3'tgggttccttccagttcg Reverse: 5'-> 3'aggcgtctggtgtcgtatg	166
Ngn3	Forward: 5'-> 3'tggcactcagcaaacagcga Reverse: 5'->3'acccagagccagacaggtct	101
Beta-actin	Forward: 5'-> 3'tggcactcagcaaacagcga Reverse: 5'->3'acccagagccagacaggtct	101



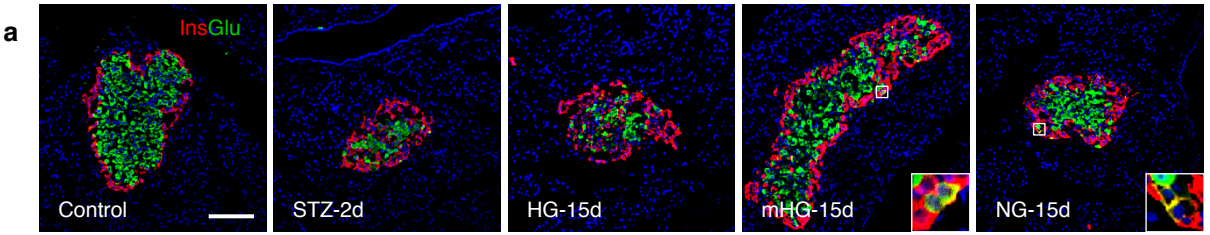
Supplementary Fig 1. Recovery from diabetes after mild hyperglycemia incubation. Eight-week-old male SD rats were treated with a single high dose of STZ (60mg/kg), and 48 hrs post STZ injection newly diabetic rats (BG>25mM) were randomly treated with: no treatment (referred as HG, n = 6), daily exogenous long-acting human insulin analogue injection that restore normoglycemia (BG<11.1mM, referred as NG, n=8), or maintained mild hyperglycemia (15mM<BG<20mM, referred as mHG, n=15). Six normal rats were used as normal control (Control). Insulin withdraw was executed within 30 days in mHG and at day 80 in NG. (a) Insulin dosages monitored for 80 days. (b) Random blood glucose level at day 90. Each point represents a single animal.



Supplementary Fig 2. Rapid beta cell regeneration after mild hyperglycemia treatment. (a) The distribution of islet sizes. The results are presented as the means ± SD. *p<0.05, **p<0.01. (b) Beta cell size measurement in rats that recovered from diabetes. Beta cell size was calculated by measuring the area of individual insulin+ cells. Cell boundaries were determined by immunostaining for E-cadherin. Each graph represents the measurements from 5 individual mice; for each rat, the size of 1000 individual beta cells was measured.



Supplementary Fig 3. Little evidence for the presence of embryonic endocrine progenitor cells in the regenerating pancreas. (a) Immunostaining for the embryonic endocrine progenitor marker Neurogenin3 (Ngn3) in embryos. Nuclei were labeled with DAPI. Scale bars, 50μm. (b) Representative islets stained with antibodies against insulin (red) and Ngn3 (green) of normal rats (Control), STZ-treated rats at day 2 (STZ-2d) and rats at day 15 after no treatment (HG-15d), mild hyperglycemia incubation (mGH-15d) and euglycemia incubation (NG-15d). Nuclei were labeled with DAPI. Scale bars, 100μm. (c) Expression of Ngn3 in isolated islets (pooled from 5 rats). The results are presented as the means ± SD.



Supplementary Fig 4. Detection of a few cells co-expressing insulin and glucagon in regenerating islets. (a) Representative islets stained with antibodies against insulin (green) and glucagon (red) of normal rats (Control), STZ-treated rats at day 2 (STZ-2d) and rats at day 15 after no treatment (HG-15d), mild hyperglycemia incubation (mGH-15d) and euglycemia incubation (NG-15d). Nuclei were labeled with DAPI. Scale bars, 100μm. The boxed regions showed the high power photomicrograph at the bottom right of the image.