

Supporting Information

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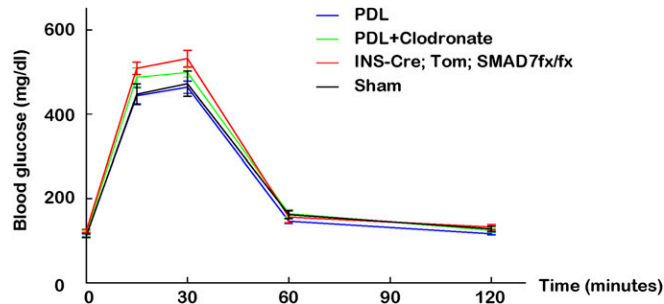


Fig. S1. Intraperitoneal glucose tolerance test (IPGTT) of the mice. IPGTT was performed in mice 1 wk after pancreatic duct ligation (PDL), with or without clodronate, or in INS-Cre; Tomato; SMAD7fx/fx mice, with controls. All of the mice seemed to have a normal glucose response.

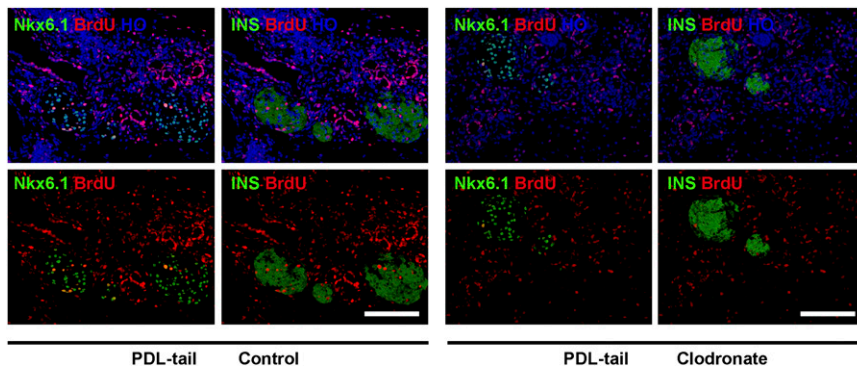


Fig. S2. Representative images of BrdU, insulin, and Nkx6.1 triple immunostaining in control and clodronate-treated pancreas. Individual color channel combinations are shown to give more detail for Fig. 2C. HO, nuclei staining. INS, insulin. (Scale bars: 50 μ m.)

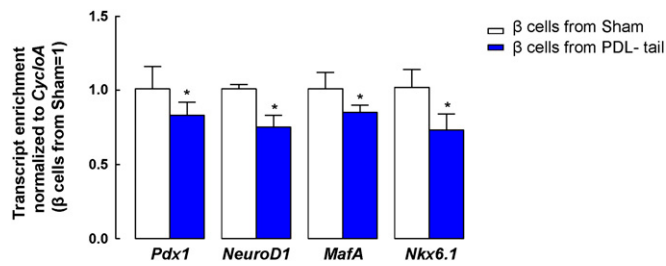


Fig. S3. Beta cells in ligated tail part of the pancreas (PDL-tail) down-regulate *Pdx1*, *NeuroD1*, *MafA*, and *Nkx6.1*. GFP⁺ beta cells were isolated from sham MIP-GFP mice, or after PDL, by FACS. Beta cells from PDL-tail down-regulate *Pdx1*, *NeuroD1*, *MafA*, and *Nkx6.1*. * $P < 0.05$.

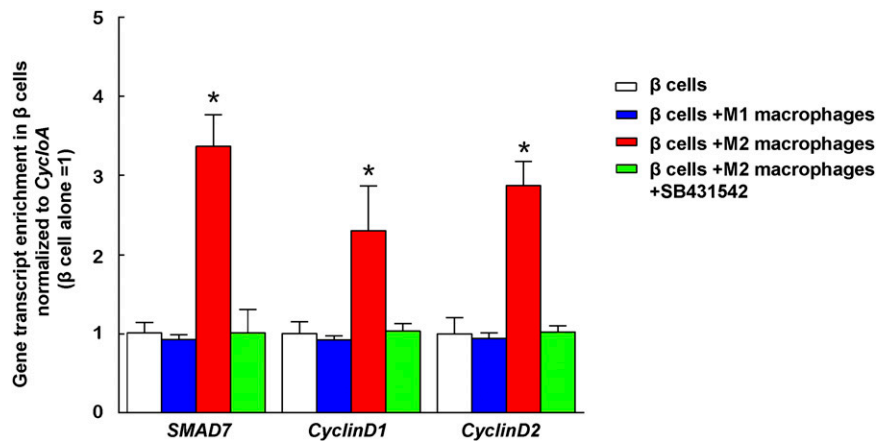


Fig. 56. Gene expression in beta cells in coculture with macrophages. Beta cells up-regulate Smad7, CyclinD1, and CyclinD2, when cocultured with M2 macrophages, but not when cocultured with M1 macrophages. The increase in SMAD7, CyclinD1, and CyclinD2 in beta cells by coculture with M2 macrophages was completely blocked by SB431542. * $P < 0.05$.

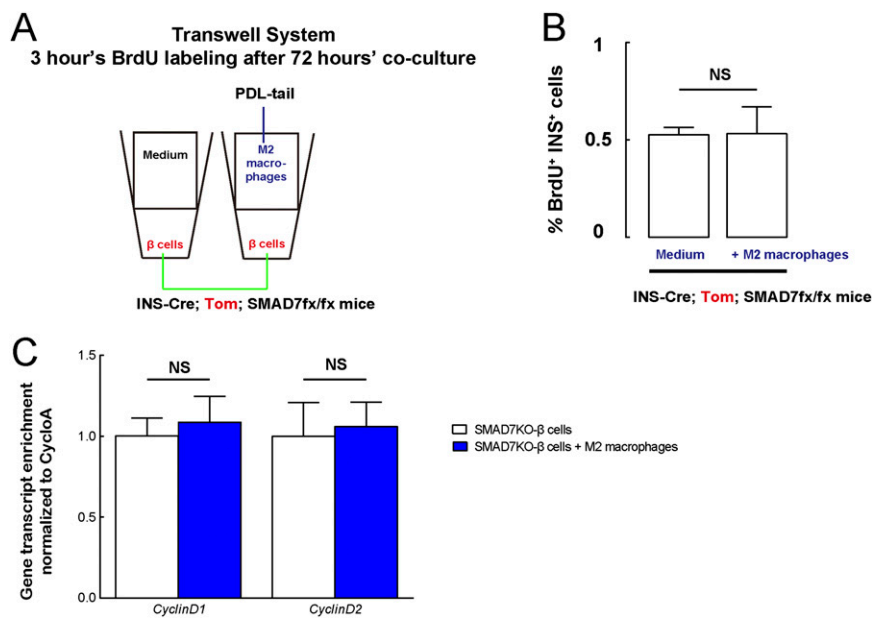


Fig. 57. SMAD7KO beta cells do not increase proliferation in the coculture with M2 macrophages. (A) Schematic showing coculture of beta cells from beta-cell-specific SMAD7KO with M2 macrophages from PDL-pancreas. (B and C) Loss of SMAD7 in beta cells resulted in loss of the increase in beta-cell proliferation (B) and failure to induce CyclinD1 and CyclinD2 in beta cells. NS, no significance.

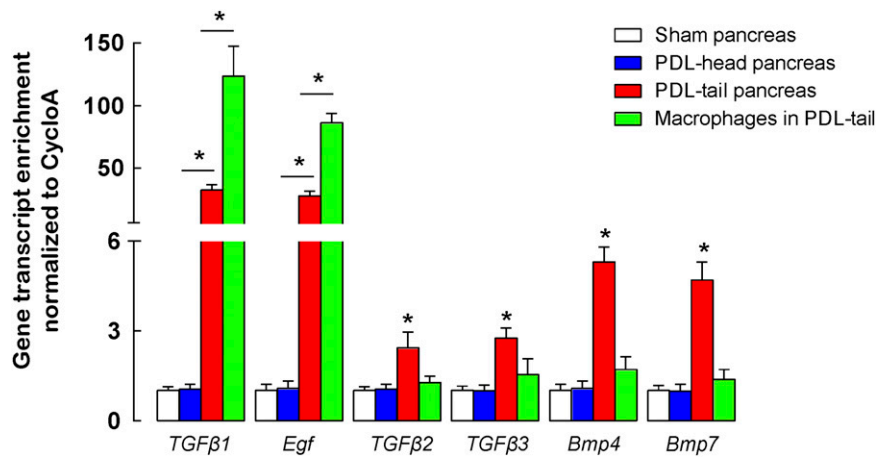


Fig. S8. M2 macrophages express significant levels of TGFβ1 and EGF in the PDL-tail pancreas. We did a screening of the candidate factors that may be released from M2 macrophages to affect beta-cell proliferation. Among numerous screened factors, we detected a significant increase in the mRNA levels of TGFβ1 and EGF in the PDL-tail pancreas, and specifically in M2 macrophages. A modest increase in TGFβ2, TGFβ3, Bmp4, and Bmp7 were also found in the PDL-tail pancreas, but the recruited macrophages seemed not to be the predominant source of them. Numerous other factors tested showed no difference, including activins. * $P < 0.05$.

Table S1. Individual data from quantification of beta cells in Fig. 1B

Mouse no.	INS ⁺ (Nkx6.1 ^{+/-}) cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ cells	INS ⁺ Nkx6.1 ⁺ cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ Nkx6.1 ⁺ cells
Sham						
1	3,152	52	1.65	3,137	51	1.63
2	5,617	50	0.89	5,602	49	0.87
3	5,376	50	0.93	5,369	48	0.89
4	4,553	51	1.12	4,521	50	1.11
5	5,882	50	0.85	5,869	48	0.82
Mean			1.09			1.06
SE			0.15			0.15
PDL-head						
1	3,517	51	1.45	3,497	50	1.43
2	3,289	50	1.52	3,278	49	1.49
3	4,065	50	1.23	4,052	49	1.21
4	3,095	52	1.68	3,082	50	1.62
5	4,906	52	1.06	4,889	51	1.04
Mean			1.39			1.36
SE			0.11			0.10
PDL-tail						
1	2,029	235	11.58	2,018	232	11.50
2	2,037	295	14.48	2,031	291	14.33
3	2,015	260	12.90	2,006	256	12.76
4	2,008	199	9.91	1,997	198	9.91
5	2,027	235	11.59	2,013	232	11.53
Mean			12.09			12.01
SE			0.76			0.74

Table S2. Individual data from quantification of beta cells in Fig. 2F

Mouse no.	INS ⁺ (Nkx6.1 ^{+/-}) cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ cells	INS ⁺ Nkx6.1 ⁺ cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ Nkx6.1 ⁺ cells
Liposome						
1	2,011	245	12.18	1,999	242	12.11
2	2,008	277	13.79	1,997	274	13.72
3	2,013	272	13.51	2,002	268	13.39
4	2,001	206	10.29	1,992	205	10.29
5	2,024	217	10.72	2,003	212	10.58
Mean			12.10			12.02
SE			0.71			0.70
Clodronate						
1	2,082	51	2.45	2,067	49	2.37
2	3,081	53	1.72	3,055	50	1.64
3	2,242	50	2.23	2,218	48	2.16
4	3,095	52	1.68	3,074	51	1.66
5	2,524	52	2.06	2,501	50	2.00
Mean			2.03			1.97
SE			0.15			0.14

Table S3. Individual data from quantification of beta cells in Fig. 4C

Mouse no.	INS ⁺ (Nkx6.1 ^{+/-}) cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ cells	INS ⁺ Nkx6.1 ⁺ cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ Nkx6.1 ⁺ cells
INS-Cre/Tom/SMAD7fx/fx						
1	6,579	50	0.76	6,517	49	0.75
2	4,808	50	1.04	4,773	49	1.03
3	4,180	51	1.22	4,128	51	1.24
4	7,083	51	0.72	6,997	49	0.70
5	2,954	52	1.76	2,909	50	1.72
Mean			1.10			1.09
SE			0.19			0.19
INS-Cre/Tom						
1	2,005	269	13.42	1,996	267	13.38
2	2,042	255	12.49	2,034	251	12.34
3	2,019	236	11.69	2,002	235	11.74
4	2,014	266	13.21	1,997	263	13.17
5	2,003	244	12.18	1,989	243	12.22
Mean			12.60			12.57
SE			0.32			0.31

Table S4. Individual data from quantification of beta cells in Fig. 5E

Mouse no.	INS ⁺ (Nkx6.1 ^{+/-}) cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ cells	INS ⁺ Nkx6.1 ⁺ cells counted	BrdU ⁺ cells counted	%BrdU ⁺ INS ⁺ Nkx6.1 ⁺ cells
AAV-GFP						
1	2,013	56	2.78	1,987	56	2.82
2	2,096	50	2.39	2,085	49	2.35
3	4,122	50	1.21	4,057	49	1.21
4	3,877	51	1.32	3,842	51	1.33
5	2,009	58	2.89	1,994	56	2.81
Mean			2.12			2.10
SE			0.36			0.35
AAV-SMAD7						
1	2,005	154	7.68	1,977	152	7.69
2	2,012	121	6.01	2,001	118	5.90
3	2,033	86	4.23	2,018	83	4.11
4	2,002	112	5.59	1,981	109	5.50
5	2,018	176	8.72	1,993	171	8.58
Mean			6.45			6.36
SE			0.79			0.80