SUPPLEMENTARY FIGURES

Supplementary Figure 1.

EndoC-βH1 cells were either mock-tranfected (control) or transfected with PolyI:C and analyzed 24 hours later. **(A, B)** Heatmap from global transcriptomic analysis and RT-qPCR data represent up-regulated PRR genes (n=3). **(C)** Heatmap from global transcriptomic analysis indicating that PolyI:C treatment induces the expression of *B2M*. Data from RT-qPCR are the means ± SD of 3 independent experiments (t-tests; **p<0.01 and ***p<0.001 relative to control.)

Supplementary Figure 2.

EndoC-βH1 cells were either mock-transfected (control) or transfected with PolyI:C and analyzed 24 hours later. β cell disallowed genes (19, 20) from global transcriptomic analysis are listed (n=3; the means ± SD of 3 independent experiments are listed)

Supplementary Figure 3.

(A-D) EndoC-βH1 cells were either mock-tranfected (control) or transfected with PolyI:C. 24 hours later, cells were stained with Annexin-V and Propidium Iodide and FAC-sorted (A, B) (n=3; Representative FACS plot of 3 independent experiment is shown). RNAs were prepared from living Annexin-V[neg] / Propidium Iodide^{neg} cells for RT-qPCR analysis (C, D). Data from FACS analyses and RT-qPCR are the means ± SD of 3 independent experiments (t-tests; *p<0.05, **p<0.01 and ***p<0.001 relative to control.)

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EndoC-βH1 cells were either mock-tranfected (control) or transfected with PolyI:C and analyzed 24 hours later. Heatmap from global transcriptomic analysis represents a list of genes previously found up-regulated in CVB5-infected human islets (10, 21).

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EndoC-βH1 cells were treated with PMA for 8 hours and RNAs were prepared for RT-qPCR analyses of *HES1*, *MYC*, *MAFA* and *SLC30A8* genes expression levels (A). EndoC-βH1 cells were treated with PMA and/or PDTC for 8 hours. RNAs were prepared for RT-qPCR (B) and proteins for Western blot analyses (C).

Data from RT-qPCR and Western blot are the means ± SD of 3 independent experiments (t-tests or ANOVA with Bonferroni's correction for multiple comparison; *<0.05 and ***p<0.001 relative to control.)

Supplementary Figure 6.

(A) EndoC-βH1 cells were treated for 72 hours with PolyI:C (1-50µg/ml) that was added (without transfection) in the culture medium. RNAs were prepared for RT-qPCR (n=3) **(B)** Conditioned medium from mock-transfected (CTRL) or PolyI:C-transfected EndoC-βH1 cells was treated with or without RNAse-A and added to naive EndoC-βH1 cells. RNAs were prepared 72 hours later, for RT-qPCR (n=3).

Data from RT-qPCR represent the means ± SD of 3 independent experiments (ANOVA with Bonferroni's correction; ***p<0.001 relative to PolyI:C treatment.)

Supplementary Figure 7.

(A) Scheme of the SOX9 constructs used for EndoC-βH1 transfection. **(B-C)** SOX9 responsive elements were co-transfected with MCS-ires-GFP, SOX9WT-ires-GFP, VP16-ires-GFP or VP16-SOX9ΔTAD-ires-GFP. Luciferase activity was measured 48h later (n=4).

Data from Luciferase assay represent the means ± SD of 4 independent experiments (ANOVA with Bonferroni's correction; **p<0.01 and ***p<0.001 relative to control.)

Supplementary Figure 8.

Venn diagram with genes up-regulated (>2 fold) in EndoC-βH1 cells treated with PolyI:C and following ectopic expression of SOX9/VP16-SOX9ΔTAD and

orthologous genes up-regulated (>2 fold) in dedifferentiated β cells from NOD mice (28). In red: genes up-regulated by both PolyI:C and SOX9/VP16-SOX9ΔTAD; In blue: genes up-regulated in NOD dedifferentiated β cells and by SOX9/VP16-SOX9ΔTAD; In green: genes up-regulated in all three sets.
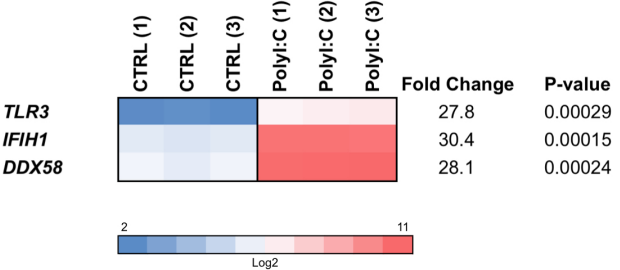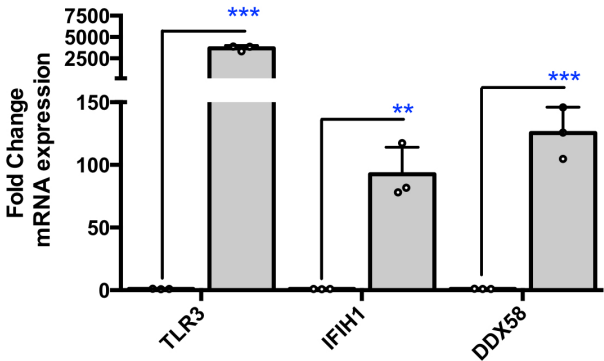
Supplementary Table 1.

Probes sequences

	Forward Sequence (5'-->3')	Reverse Sequence (5'-->3')
ACTB	CTGTACGCCAACACAGTGCT	GCTCAGGAGGAGCAATGATC
CTGF	CAAGGGCCTCTTCTGTGACTT	GGTACACCGTACCACCGAAG
DDX58	TGACTGGACGTGGCAAAACA	CAGCAACTGAGGTGGCAATC
DEPTOR	CTTCTGACAGAGAGACGGCA	CCGTCATCCTTTCTAAAGCGG
G6PC2	CCATGCCTTGAACAGTTCCC	GCCAGATGGACTTCCTGGAC
HES1	GTCAACACGACACGGGATAAACC	TTTCCAGAATGTCCGCCTTCTCC
IFIH1	GCATGGAGGAGGAACTGTTGA	CCAGTTTTCTTTCTGCACAATCCT
IFNA2	AAACCCACAGCCTGGGTAGC	CAGGGATGGTTTCAGCCTTTTGG
IFNB	GTTGAGAACCTCCTGGCTAATG	GGTAATGCAGAATCCTCCCATAATA
IL6	CCAGAGCTGTGCAGATGAGT	GGGTCAGGGGTGGTTATTGC
IL8	AAATCTGGCAACCCTAGTCTG	GTGAGGTAAGATGGTGGCTAAT
INS	TGTCCTTCTGCCATGGCCCT	TTCACAAAGGCTGCGGCTGG
INS pre-mRNA	GTGAACCAACACCTGTGCGG	AGGGGCAGCAATGGGCAGTT
LRRTM2	CCAACTCCCTGCGGACTATC	GCAAATCCATTGCGAGCCAA
MAFA	ATTCTGGAGAGCGAGAAGTGCCAA	CGCCAGCTTCTCGTATTTCTCCTT
MAFB	CACCACCTGGAGAATGAGAAG	TTCTCGCACTTGACCTTGTAG
MAML2	TGGGATAAACGGAGAGCAGC	CATTGGGTCGCTTGCTGTTG
MYC	GTAGTGGAAAACCAGCAGCC	AGAAATACGGCTGCACCGAG
NEUROD1	ATTGCACCAGCCCTTCCTTTGATG	TCGCTGCAGGATAGTGCATGGTAA
NKX6-1	GAAGAGGACGACGACTACAATAAG	CTGCTGGACTTGTGCTTCT
PDX1	TACTGGATTGGCGTTGTTTGTGGC	AGGGAGCCTTCCAATGTGTATGGT
PPIA	ATGGCAAATGCTGGACCCAACA	ACATGCTTGCCATCCAACCACT
RELA	TGAGCCCACAAAGCCTTATC	ACAATGCCAGTGCCATACA
SLC2A2	AGCTGCATTCAGCAATTGGACCTG	ATGTGAACAGGGTAAAGGCCAGGA
SLC30A8	ACAGCCAAGTGGTTCGGAGAGAAA	TTGGGAAACTGACGGTGTGACTGA
SOX9	TTCACCTACATGAACCCCGC	AAGGTCGAGTGAGCTGTGTG
TLR3	GCGCTAAAAAGTGAAGAACTGGA	TTGCGTGAAAACACCCTGGA
TNFA	GATCCCTGACATCTGGAATCTG	GAAACATCTGGAGAGAGGAAGG

Supplementary Figure 1.

A

	CTRL (1)	CTRL (2)	CTRL (3)	PolyI:C (1)	PolyI:C (2)	PolyI:C (3)	Fold Change	P-value
TLR3							27.8	0.00029
IFIH1							30.4	0.00015
DDX58							28.1	0.00024

2   11
Log2

B

C

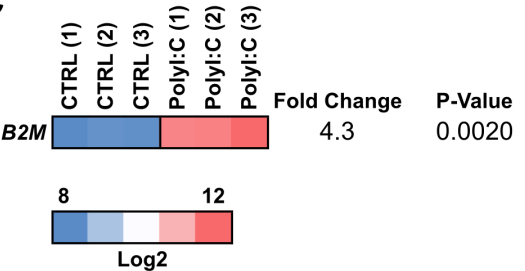|	CTRL (1)	CTRL (2)	CTRL (3)	PolyI:C (1)	PolyI:C (2)	PolyI:C (3)	Fold Change	P-Value
B2M							4.3	0.0020

8   12
Log2

Supplementary Figure 1.

EndoC-βH1 cells were either mock-tranfected (control) or transfected with PolyI:C and analyzed 24 hours later. **(A, B)** Heatmap from global transcriptomic analysis and RT-qPCR data represent up-regulated PRR genes (n=3). **(C)** Heatmap from global transcriptomic analysis indicating that PolyI:C treatment induces the expression of *B2M*. Data from RT-qPCR are the means ± SD of 3 independent experiments (t-tests; **p<0.01 and ***p<0.001 relative to control.)
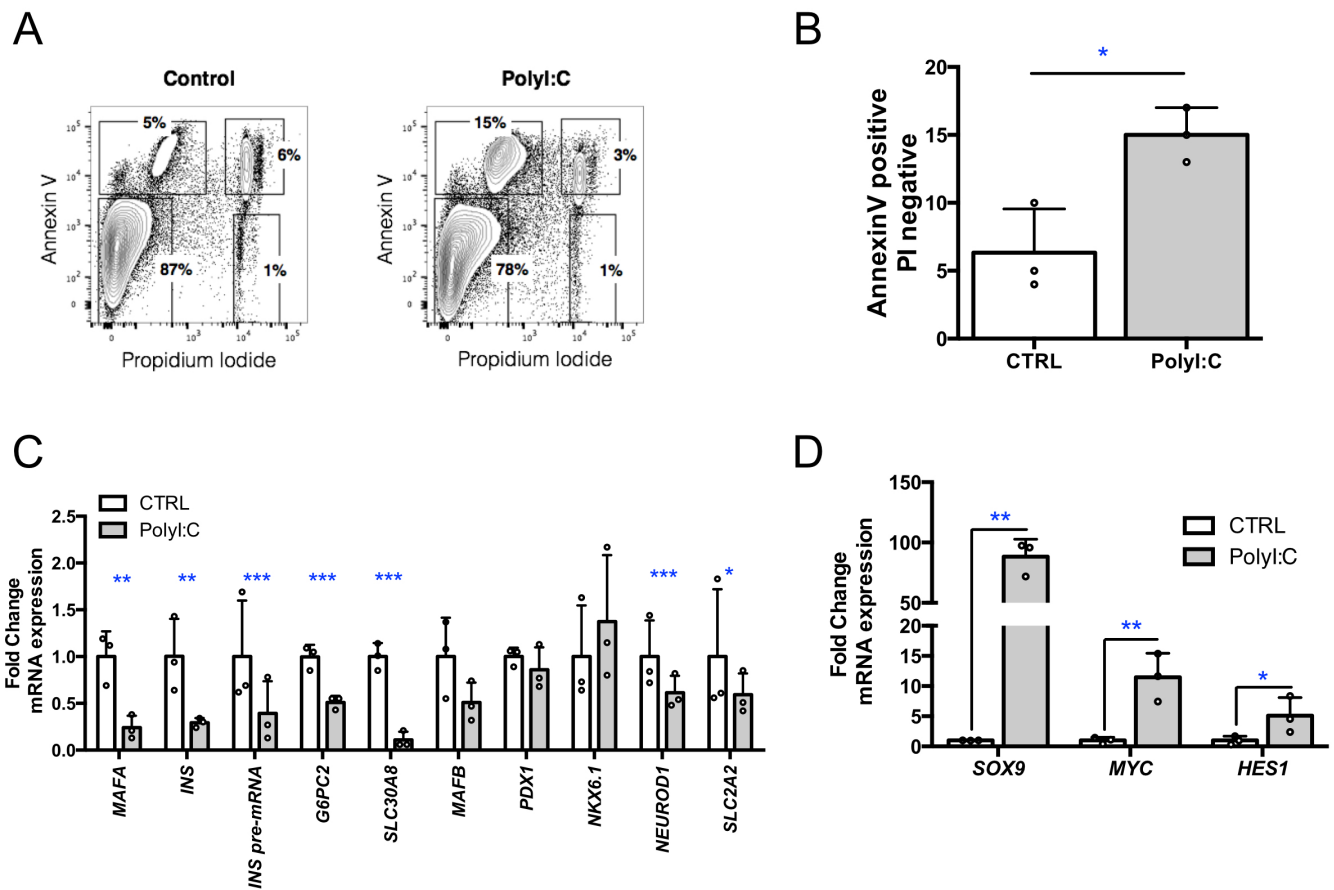
Supplementary Figure 2.

	Fold Change Polyl:C vs CTRL	P-Value
LRIG3	4.04 (±0.28)	0.0002
LMO4	2.28 (±0.04)	0.0003
TPM2	1.74 (±0.27)	0.0206
DAPK2	1.65 (±0.35)	0.0022
GAREM	1.45 (±0.17)	0.0104
RPL36	1.37 (±0.51)	0.0839
ZCCHC24	1.27 (±0.26)	0.0598
PLEC1	1.23 (±0.15)	0.0605
ACOT7	1.19 (±0.12)	0.0526
SMOC2	1.18 (±0.35)	0.2214
ITIH5	1.12 (±0.13)	0.1191
FAM13A	1.12 (±0.19)	0.1886
IGFBP4	1.09 (±0.05)	0.0331
SLC16A1	1.07 (±0.19)	0.2753
MGLL	1.04 (±0.20)	0.3655
ZDHHC9	1.02 (±0.03)	0.1641
COX5A	1.01 (±0.15)	0.4252
NFIB	1.01 (±0.02)	0.2103
HPGD	1.00 (±0.06)	0.4011
MGST1	1.00 (±0.09)	0.4553
RARRES2	0.98 (±0.15)	0.4350
TGM2	0.96 (±0.03)	0.1435
HSD11B1	0.96 (±0.04)	0.1229
GAS6	0.94 (±0.03)	0.0331
PDGFRA	0.91 (±0.18)	0.2788
YAP1	0.91 (±0.12)	0.1761
LDHA	0.88 (±0.19)	0.2256
NDRG2	0.87 (±0.08)	0.0691
IGF1	0.85 (±0.00)	0.0001
TRF	0.84 (±0.07)	0.0383
RASGRP2	0.84 (±0.13)	0.1075
TST	0.80 (±0.05)	0.0118
GAS1	0.80 (±0.14)	0.0771
OLFML1	0.73 (±0.14)	0.0566
FCGRT	0.66 (±0.14)	0.0406

Supplementary Figure 2.

EndoC-βH1 cells were either mock-transfected (control) or transfected with Polyl:C and analyzed 24 hours later. β cell disallowed genes (19, 20) from global transcriptomic analysis are listed (n=3; the means ± SD of 3 independent experiments are listed)

Supplementary Figure 3.

A

B

C

D

Supplementary Figure 3.

(A-D) EndoC-βH1 cells were either mock-tranfected (control) or transfected with PolyI:C. 24 hours later, cells were stained with Annexin-V and Propidium Iodide and FAC-sorted (A, B) (n=3; Representative FACS plot of 3 independent experiment is shown). RNAs were prepared from living Annexin-V[neg] / Propidium Iodide^{neg} cells for RT-qPCR analysis (C, D). Data from FACS analyses and RT-qPCR are the means ± SD of 3 independent experiments (t-tests; *p<0.05, **p<0.01 and ***p<0.001 relative to control.)

Supplementary Figure 4.

Antiviral Responses	CTRL (1)	CTRL (2)	CTRL (3)	PolyI:C (1)	PolyI:C (2)	PolyI:C (3)	Fold Change	P-value
MX1							270.0	0.0002
OASL							126.9	0.0002
OAS1							39.0	0.0000
IFI44							21.8	0.0040
OAS3							21.7	0.0001
OAS2							15.8	0.0019
MX2							13.3	0.0004
ZC3HAV1							8.8	0.0001
CD68							7.7	0.0002
PTX3							4.7	0.0381
ADAR							3.9	0.0002
EIF2AK2							3.8	0.0003
PVRL2							2.8	0.0027
TNIP1							2.2	0.0055

Chemokines

	CTRL (1)	CTRL (2)	CTRL (3)	PolyI:C (1)	PolyI:C (2)	PolyI:C (3)	Fold Change	P-value
CXCL10							680.1	0.0000
CXCL11							104.8	0.0003
CCL5							70.2	0.0001
CCL4							25.4	0.0013
CXCL9							16.5	0.0019
CXCL1							12.1	0.0152
CX3CL1							8.2	0.0004
CXCL2							5.8	0.0010
CXCL3							3.6	0.0008

Signal Transduction and Transcription

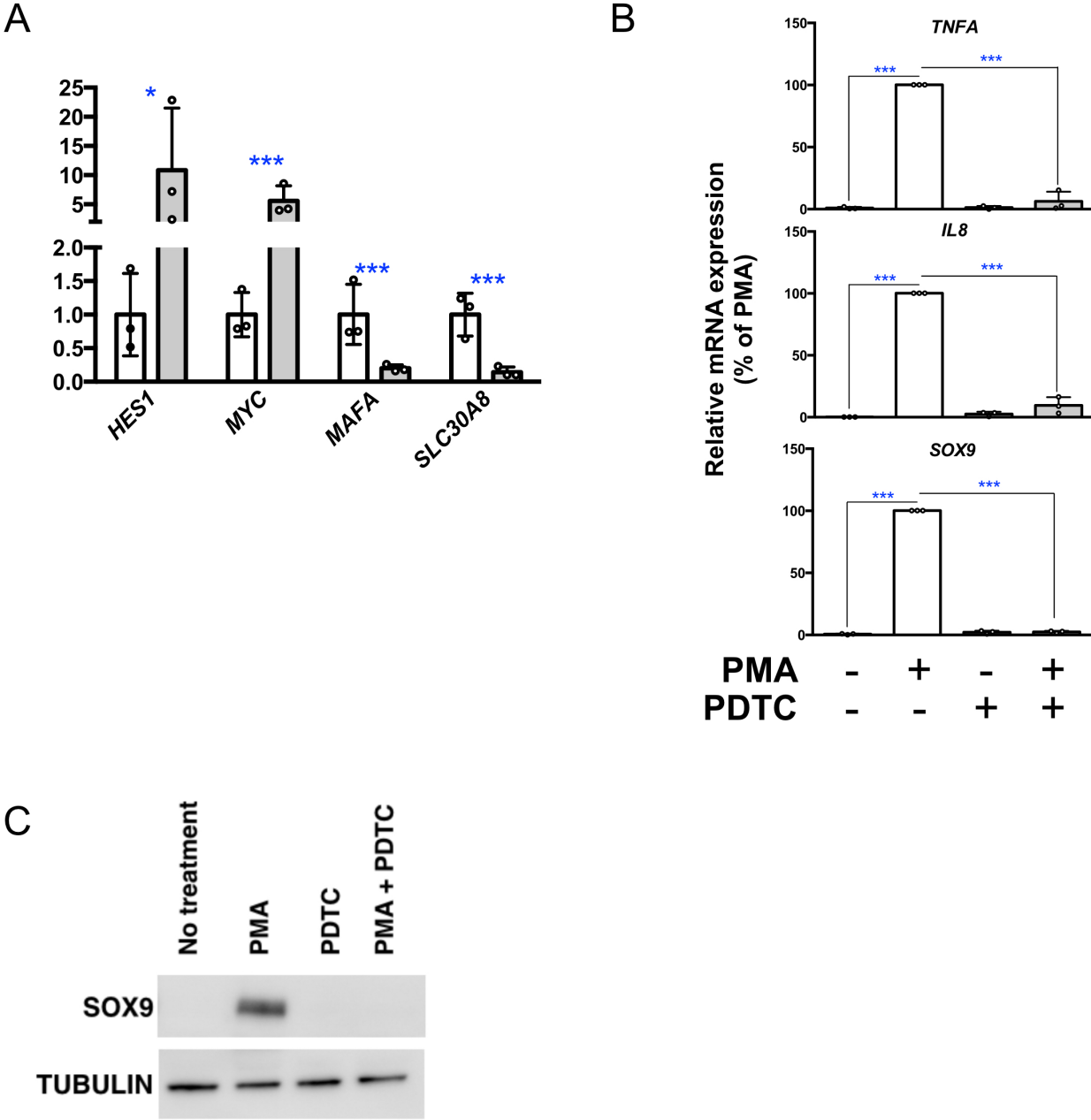|	CTRL (1)	CTRL (2)	CTRL (3)	PolyI:C (1)	PolyI:C (2)	PolyI:C (3)	Fold Change	P-value
IRF1							27.4	0.0004
NMI							22.6	0.0001
STAT1							16.0	0.0002
JAK2							13.8	0.0001
STAT2							8.6	0.0001
ATF3							8.4	0.0006
IRF7							6.7	0.0031
IRF2							4.9	0.0001
ATF5							2.6	0.0004

2   12

Log2

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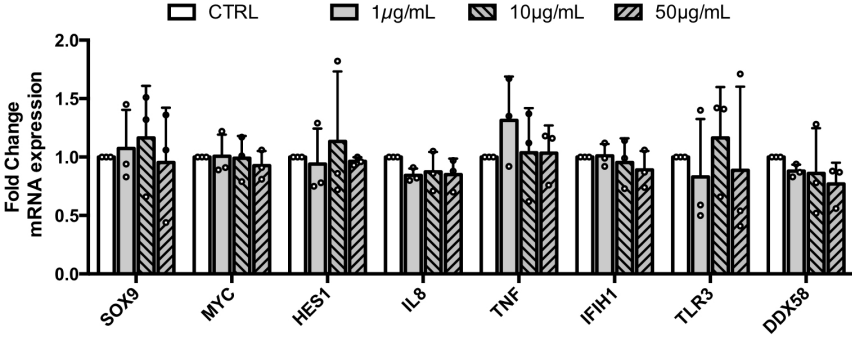# Supplementary Figure 5.

A

B

C

Supplementary Figure 5.

EndoC-βH1 cells were treated with PMA for 8 hours and RNAs were prepared for RT-qPCR analyses of *HES1*, *MYC*, *MAFA* and *SLC30A8* genes expression levels (A). EndoC-βH1 cells were treated with PMA and/or PDTC for 8 hours. RNAs were prepared for RT-qPCR (B) and proteins for Western blot analyses (C).
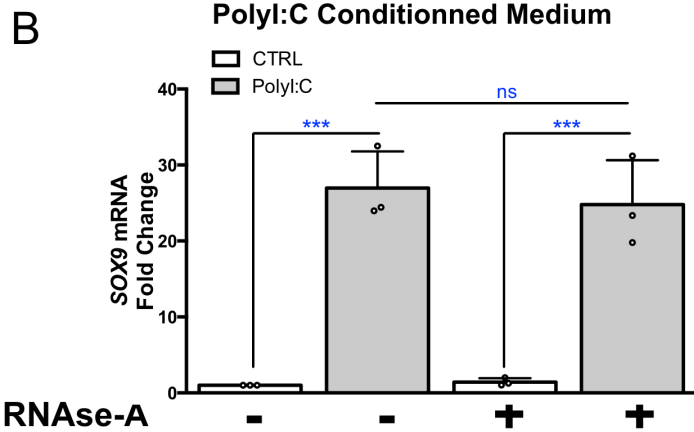
Data from RT-qPCR and Western blot are the means ± SD of 3 independent experiments (t-tests or ANOVA with Bonferroni's correction for multiple comparison; *<0.05 and ***p<0.001 relative to control.)

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A

B

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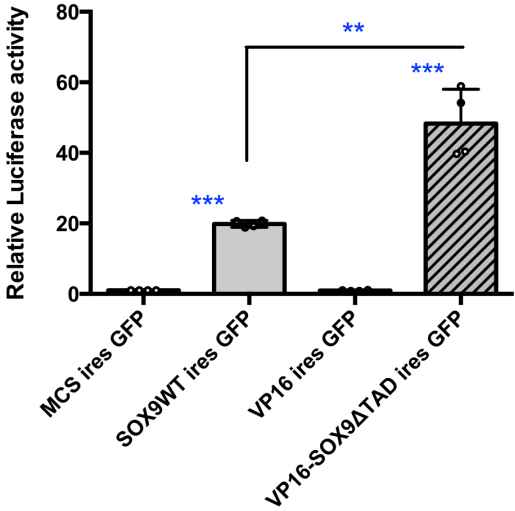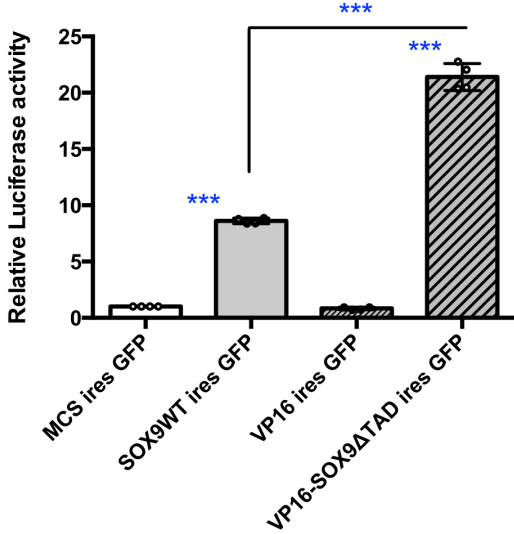
Supplementary Figure 7.

A

B

SOX9 responsive element activity
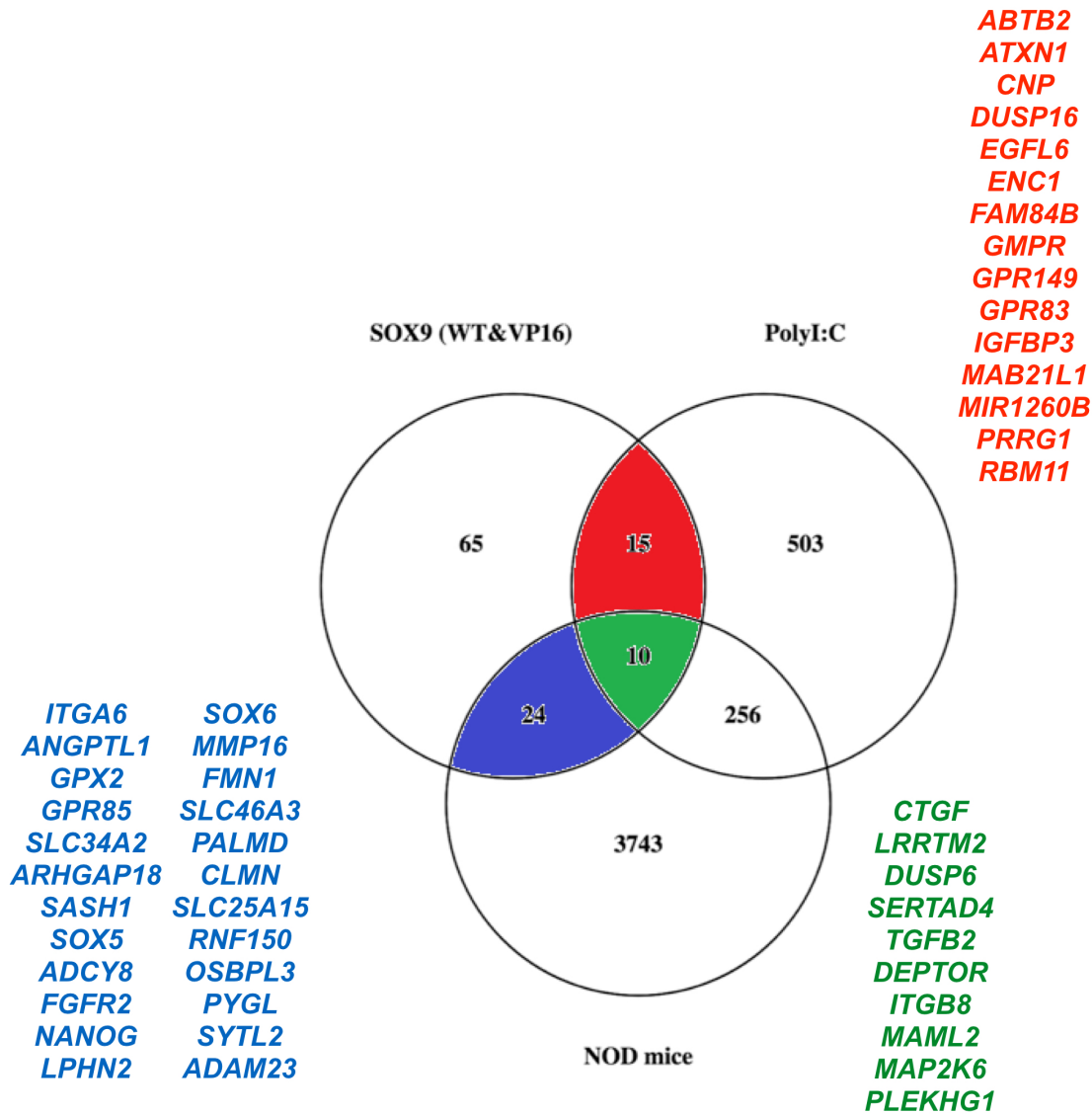**(*Col2A1* promoter)**

C

SOX9 responsive element activity
(SOX9 binding motif)

Supplementary Figure 7.

(A) Scheme of the SOX9 constructs used for EndoC-βH1 transfection. **(B-C)** SOX9 responsive elements were co-transfected with MCS-ires-GFP, SOX9WT-ires-GFP, VP16-ires-GFP or VP16-SOX9ΔTAD-ires-GFP. Luciferase activity was measured 48h later (n=4).

Data from Luciferase assay represent the means ± SD of 4 independent experiments (ANOVA with Bonferroni's correction; **p<0.01 and ***p<0.001 relative to control.)

Supplementary Figure 8.

SOX9 (WT&VP16)   PolyI:C

65   15   503

10

24   256

3743

NOD mice

ITGA6   SOX6
ANGPTL1   MMP16
GPX2   FMN1
GPR85   SLC46A3
SLC34A2   PALMD
ARHGAP18   CLMN
SASH1   SLC25A15
SOX5   RNF150
ADCY8   OSBPL3
FGFR2   PYGL
NANOG   SYTL2
LPHN2   ADAM23

CTGF
LRRTM2
DUSP6
SERTAD4
TGFB2
DEPTOR
ITGB8
MAML2
MAP2K6
PLEKHG1

Supplementary Figure 8.

Venn diagram with genes up-regulated (>2 fold) in EndoC-βH1 cells treated with PolyI:C and following ectopic expression of SOX9/VP16-SOX9ΔTAD and orthologous genes up-regulated (>2 fold) in dedifferentiated β cells from NOD mice (28). In red: genes up-regulated by both PolyI:C and SOX9/VP16-SOX9ΔTAD; In blue: genes up-regulated in NOD dedifferentiated β cells and by SOX9/VP16-SOX9ΔTAD; In green: genes up-regulated in all three sets.