**Supplemental Data.**

# PTPN2 regulates the interferon signalling and endoplasmic reticulum stress response in pancreatic β-cells in autoimmune diabetes

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| Exp ID | Age (Years) | Gender | BMI (kg/m$^2$) | Cause of death |
|---|---|---|---|---|
| **#1** | 87 | M | 35,1 | Trauma |
| **#2** | 75 | F | 27,3 | Vascular |
| **#3** | 46 | F | 25,4 | Anoxia |

**Supplementary Table S1. Pancreas organ donor characteristics for ER stress in dispersed human islets (Figure 5F).**

| Stage | Compound | Final concentration | Company |
|---|---|---|---|
| 1 (3 days, change medium every day) | MCDB131 no Glutamine | | Life Technologies, #10372-019 |
| | GlutaMAX | 2mM | Thermo Fisher, #35050 |
| | NaHCO3 | 1.5g/l | Merck Millipore, #1063290500 |
| | BSA fV | 0.5% | Sigma, #A7030 |
| | Glucose | 10mM | Sigma, #G8769 |
| | Activin A | 100ng/ml | PeproTech, #120-14E |
| | CHIR | 5µM (day 1), 0.5µM (day 2) | Axon Medchem, #1386 |
| 2 (3 days, change medium every day) | MCDB131 no Glutamine | | Life Technologies, #10372-019 |
| | GlutaMAX | 2mM | Thermo Fisher, #35050 |
| | NaHCO3 | 1.5g/l | Merck Millipore, #1063290500 |
| | BSA fV | 0.5% | Sigma, #A7030 |
| | Glucose | 10mM | Sigma, #G8769 |
| | L-Ascorbic acid | 0.25mM | Sigma, #A4554 |
| | FGF-7 | 50ng/mL | PeproTech, #100-19 |
| 3 (2 days, change medium every day) | MCDB131 no Glutamine | | Life Technologies, #10372-019 |
| | GlutaMAX | 2mM | Thermo Fisher, #35050 |
| | NaHCO3 | 2.5g/l | Merck Millipore, #1063290500 |
| | BSA fV | 2% | Sigma, #A7030 |
| | Glucose | 10mM | Sigma, #G8769 |
| | L-Ascorbic acid | 0.25mM | Sigma, #A4554 |
| | FGF-7 | 50ng/mL | PeproTech, #100-19 |
| | SANT-1 | 0.25 µM | Sigma, #S4572 |
| | Retinoic acid (RA) | 1µM | Sigma, #R2625 |
| | LDN-193189 | 100nM | Selleckchem, #S2618 |
| | ITS-X | 1:200 | Thermo Fisher, #51500056 |
| | TPB | 200nM | Santa Cruz, #SC-204424 |
| 4 (4 days, change medium every day) | MCDB131 no Glutamine | | Life Technologies, #10372-019 |
| | GlutaMAX | 2mM | Thermo Fisher, #35050 |
| | NaHCO3 | 2.5g/l | Merck Millipore, #1063290500 |
| | BSA fV | 2% | Sigma, #A7030 |
| | Glucose | 10mM | Sigma, #G8769 |
| | L-Ascorbic acid | 0.25mM | Sigma, #A4554 |
| | FGF-7 | 50 ng/mL | PeproTech, #100-19 |
| | SANT-1 | 0.25µM | Sigma, #S4572 |
| | Retinoic acid (RA) | 0.1µM | Sigma, #R2625 |
| | LDN-193189 | 200nM | Selleckchem, #S2618 |
| | EGF | 100ng/ml | StemCell Technologies, #78006 |
| | Nicotinamide | 10mM | Sigma, #N3376 |
| | Activin A | 10ng/ml | PeproTech, #120-14E |
| 5 (4 days, change medium every day) | MCDB131 no Glutamine | | Life Technologies, #10372-019 |
| | GlutaMAX | 2mM | Thermo Fisher, #35050 |
| | NaHCO3 | 1.5g/l | Merck Millipore, #1063290500 |
| | BSA fV | 2% | Sigma, #A7030 |
| | Glucose | 20mM | Sigma, #G8769 |
| | ITS-X | 1:200 | Thermo Fisher, #51500056 |
| | Heparin | 10µg/mL | StemCell Technologies, #07980 |
| | Zinc Sulfate | 10µM | Sigma, #Z0251 |
| | Retinoic acid (RA) | 0.05µM | Sigma, #R2625 |
| | SANT-1 | 0.25µM | Sigma, #S4572 |
| | LDN-193189 | 100nM | Selleckchem, #S2618 |
| | GC-1 | 1µM | Tocris, #4554 |
| | GSiXX | 100nM | Merck Millipore, #565790 |
| | ALK5inhII | 10µM | ENZO, #ALX-270-445 |
| | Betacellulin | 20ng/ml | PeproTech, #100-50 |
| | Penicillin - Streptomycin | 100U/ml - 0.1mg/ml | Sigma, #P4333 |
| | ROCK inhibitor Y-27632 | 10µM | StemCell Technologies, #72304 |
| | Heparin | 10ng/ml | StemCell Technologies, #07980 |
| 6 (7-8 days, change medium every second day) | MCDB131 no Glutamine | | Life Technologies, #10372-019 |
| | GlutaMAX | 2mM | Thermo Fisher, #35050 |
| | NaHCO3 | 1.5g/l | Merck Millipore, #1063290500 |
| | BSA fV | 2% | Sigma, #A7030 |
| | Glucose | 20mM | Sigma, #G8769 |
| | ITS-X | 1:200 | Thermo Fisher, #51500056 |
| | Heparin | 10µg/mL | StemCell Technologies, #07980 |
| | Zinc Sulfate | 10µM | Sigma, #Z0251 |
| | LDN-193189 | 100nM | Selleckchem, #S2618 |
| | ALK5inhII | 10µM | ENZO, #ALX-270-445 |
| | GC-1 | 1µM | Tocris, #4554 |
| | GSiXX | 100nM | Merck Millipore, #565790 |
| | Penicillin - Streptomycin | 100U/ml - 0.1mg/ml | Sigma, #P4333 |
| 7 (8 days, change medium every second day) | MCDB131 no Glutamine | | Life Technologies, #10372-019 |
| | GlutaMAX | 2mM | Thermo Fisher, #35050 |
| | NaHCO3 | 1.5g/l | Merck Millipore, #1063290500 |
| | BSA fV | 2% | Sigma, #A7030 |
| | Glucose | 20mM | Sigma, #G8769 |
| | ITS-X | 1:200 | Thermo Fisher, #51500056 |
| | Heparin | 10µg/mL | StemCell Technologies, #07980 |
| | Zinc Sulfate | 10µM | Sigma, #Z0251 |
| | GC-1 | 1µM | Tocris, #4554 |
| | Trolox | 10µM | Sigma, #238813 |
| | JNKi (SP600125) | 20µM | Selleckchem, #SP600125 |
| | RSV | 75µM | Sigma, #R5010 |
| | R428 | 2µM | Selleckchem, #S2841 |
| | N-acetyl-cystein (NAC) | 1mM | Sigma, #A9165 |
| | Penicillin - Streptomycin | 100U/ml - 0.1mg/ml | Sigma, #P4333 |

**Supplementary Table S2. List of molecules used for stem cell differentiation into β-like cells.**

| Antibody | Company | Reference | Dilution |
|---|---|---|---|
| | | | **Western blot** |
| PTPN2 | R&D Systems | MAB1930 | 1:300 |
| PTPN2 | Sigma-Aldrich | HPA015004 | 1:1000 |
| pSTAT1 (Y701) | Cell Signaling | 7649 | 1:1000 |
| STAT1 | Cell Signaling | 14994 | 1:1000 |
| STAT1 | Cell Signaling | 9176 | 1:1000 |
| pSTAT3 (Y705) | Cell Signaling | 9131 | 1:1000 |
| STAT3 | Cell Signaling | 9139 | 1:1000 |
| IκBα | Cell Signaling | 9242 | 1:1000 |
| BiP | Cell Signaling | 3177 | 1:1000 |
| ATF3 | Santa Cruz Biotechnology | SC-188 | 1:500 |
| ATF4 | Cell Signaling | 11815 | 1:1000 |
| peIF2α | Cell Signaling | 3597 | 1:1000 |
| Cleaved caspase 3 | Cell Signaling | 9661 | 1:300 |
| GAPDH | Trevigen | 2275-PC-100 | 1:5000 |
| α-tubulin | Sigma-Aldrich | T5168 | 1:5000 |
| β-actin | Sigma-Aldrich | A1978 | 1:2000 |
| Anti-Mouse IgG HRP | Dako | P0447 | 1:5000 |
| Anti-Rabbit IgG HRP | Dako | P0448 | 1:5000 |
| | | | **Immunofluorescence** |
| PTPN2 | Sigma-Aldrich | HPA015004 | 1:100/1:250 |
| GRP94 | Thermo Fisher | MA3016 | 1:200 |
| BiP/GRP78 Alexa fluor 488 | Thermo Fisher | PA1-014A-A488 | 1:100 |
| MANF | Sigma-Aldrich | ABN306 | 1:500 |
| OCT4-A | Cell Signaling | 2840 | 1:400 |
| SOX17 | R&D systems | AF1924 | 1:400 |
| NKX6.1 | BD Biosciences | 563022 | 1:250 |
| PDX1 | R&D systems | AF2419 | 1:500 |
| Insulin (cells) | Dako | IR002 | 1:500 |
| Insulin (pancreas slides) | Dako | A0564 | 1:5000 |
| Glucagon | Sigma | G2654 | 1:1000 |
| OCT4 | Santa Cruz Biotechnology | SC-9081 | 1:500 |
| TRA-1-60 | Thermo Fisher | MA1-023 | 1:250 |
| SSEA4 | Thermo Fisher | MA1-021-D488 | 1:250 |
| Anti-Mouse-Alexa 488 | Thermo Fisher | A21202 | 1:500/1:1000 |
| Anti-Rabbit-Alexa 488 | Thermo Fisher | A21206 | 1:500/1:1000 |
| Anti-Rat-Alexa 488 | Thermo Fisher | A11006 | 1:1000 |
| Anti-Guinea pig-Alexa 488 | Thermo Fisher | A11073 | 1:500/1:1000 |
| Anti-Mouse-Alexa 555 | Thermo Fisher | A32773 | 1:500/1:1000 |
| Anti-Rabbit-Alexa 555 | Thermo Fisher | A32794 | 1:500/1:1000 |
| Anti-Guinea-Pig-Alexa 555 | Thermo Fisher | A21435 | 1:1000 |
| Anti-Goat-Alexa 555 | Thermo Fisher | A32816 | 1:500 |
| Anti-Guinea-Pig-Alexa 568 | Thermo Fisher | A11075 | 1:500 |
| Anti-Goat-Alexa 568 | Thermo Fisher | A11057 | 1:500 |

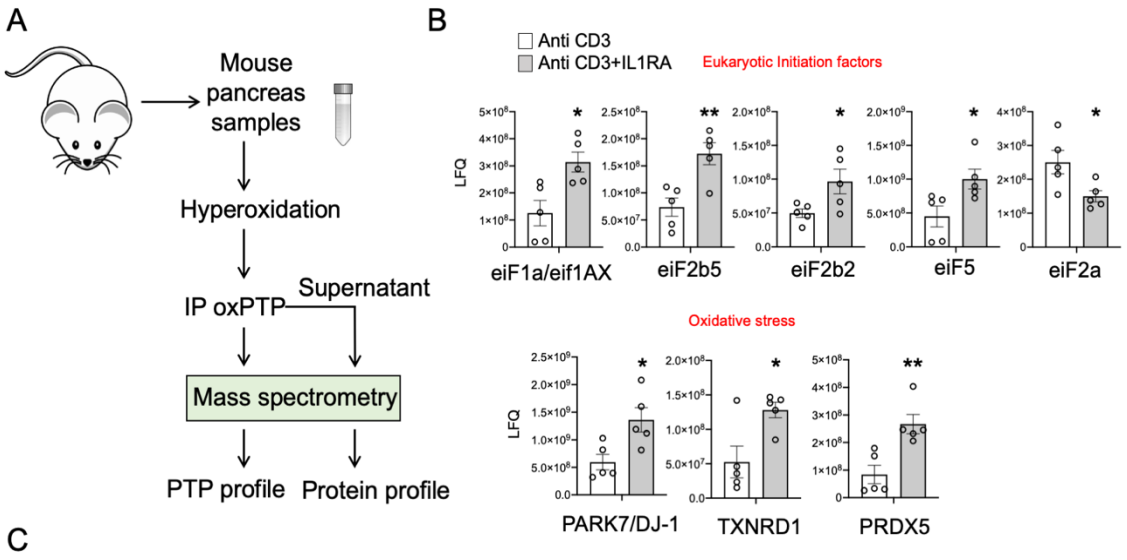
**Supplementary Table S3. List of antibodies used for Western blot and immunofluorescence analysis.**

| siRNA name | Company/catalogue number | Sequence (5’ -> 3’) |
|---|---|---|
| PTPN2 #1 | Life Technologies-Ambion, 4390824 | GGAGAUUCUAGUAUACAGA |
| PTPN2 #2 | Life Technologies-Ambion, 4427038 | GUACAGGACUUUCCUCUAA |
| PTPN2 #3 | Qiagen, Hilden, Germany, SI02225895 | CCGCTGTACTTGGAAATTCGA |
| PTPN2 #4 | Qiagen, Hilden, Germany, SI02759239 | CACAAAGGAGTTACATCTTAA |
| PTPN2 #5 | Qiagen, Hilden, Germany, SI04898222 | CAGGGTCCACTTCCTAACACA |
| PTPN2 #6 | Qiagen, Hilden, Germany, SI04950400 | TCCCATGACTATCCTCATAGA |
| STAT1 | Life Technologies-Invitrogen, STAT1HSS110273 | GGAUUGAAAGCAUCCUAGAACUCAU |
| STAT3 | Qiagen, Hilden, Germany, SI02662338 | CAGCCTCTCTGCAGAATTCAA |

**Supplementary Table S4. List of siRNAs for knockdown experiments.**

| Gene name | Primer sequences or catalogue number |
|---|---|
| PTPN2 (Human) | F: ATCGAGCGGGAGTTCGA<br>R: TCTGGAAACTTGGCCACTC |
| PTPN2 (Mouse) | F: TCTGGAAACTTGGCCACTC<br>R: ATCGAGCGGGAGTTCGA |
| CXCL9 (Human) | F: GAGGGCAAGAGCCACAGTAT<br>R: GCCATCCTGCCCATAACA |
| CXCL10 (Human) | F: GTGGCATTCAAGGAGTACCTC<br>R: GCCTTCGATTCTGGATTCAG |
| HLA-A (Human) | F: CAGGAGACACGGAATGTGAA<br>R: TTATCTGGATGGTGTGAGAACC |
| STAT1(Human) | F: GACCCAATCCAGATGTCTATGA<br>R: CCCGACTGAGCCTGATTA |
| STAT3(Human) | F: CTTTGAGACCGAGGTGTATCACC<br>R: GGTCAGCATGTTGTACCACAGG |
| BiP (Human) | QT00096404 (Qiagen, Hilden, Germany) |
| CHOP (Human) | QT00082278 (Qiagen, Hilden, Germany) |
| ATF3 (Human) | F: GCTGTCACCACGTGCAGTAT<br>R: TTTGTGTTAACGCTGGGAGA |
| ATF4 (Human) | F: GTCCTGTCCTCCACTCCAGA<br>R: AGGGATCATGGCAACGTAAG |
| Insulin (Human) | F: CCAGCCGCAGCCTTTGTGA<br>R: CCAGCTCCACCTGCCCCA |
| OCT4 (Human) | F: TTGGGCTCGAGAAGGATGTG<br>R: TGCATAGTCGCTGCTTGATC |
| SOX2 (Human) | F: GCCCTGCAGTACAACTCCAT<br>R: TGCCCTGCTGCGAGTAGG |
| NANOG(Human) | F: CTCAGCCTCCAGCAGATGC<br>R: TAGATTTCATTCTCTGGTTCTGG |
| PTPN2 Exon ¾ (Human) | F: TCACAGTCGTGTTAAACTGCA<br>R: CTGCTTTGGTCTTCTGCTGC |
| PPIG (Human) | F: TCTTGTCAATGGCCAACAGAG<br>R: GCCCATCTAAATGAGGAGTTG |
| GAPDH (Human) | F: CAGCCTCAAGATCATCAGCA<br>R: TGTGGTCATGAGTCCTTCCA |
| β-actin (Human) | F: CTGTACGCCAACACAGTGCT<br>R: GCTCAGGAGGAGCAATGATC |
| β-actin (Mouse) | F: ACGGCCAGGTCATCACTATT<br>R: GTTGGCATAGAGGTCTTTACG |

**Supplementary Table S5. List of probes used for qPCR.** Real-time quantitative PCR was performed using the Biorad CFX96 machine (Biorad, Hercules, CA) and the SYBR green PCR Master Mix (Biorad). F: forward R: reverse.

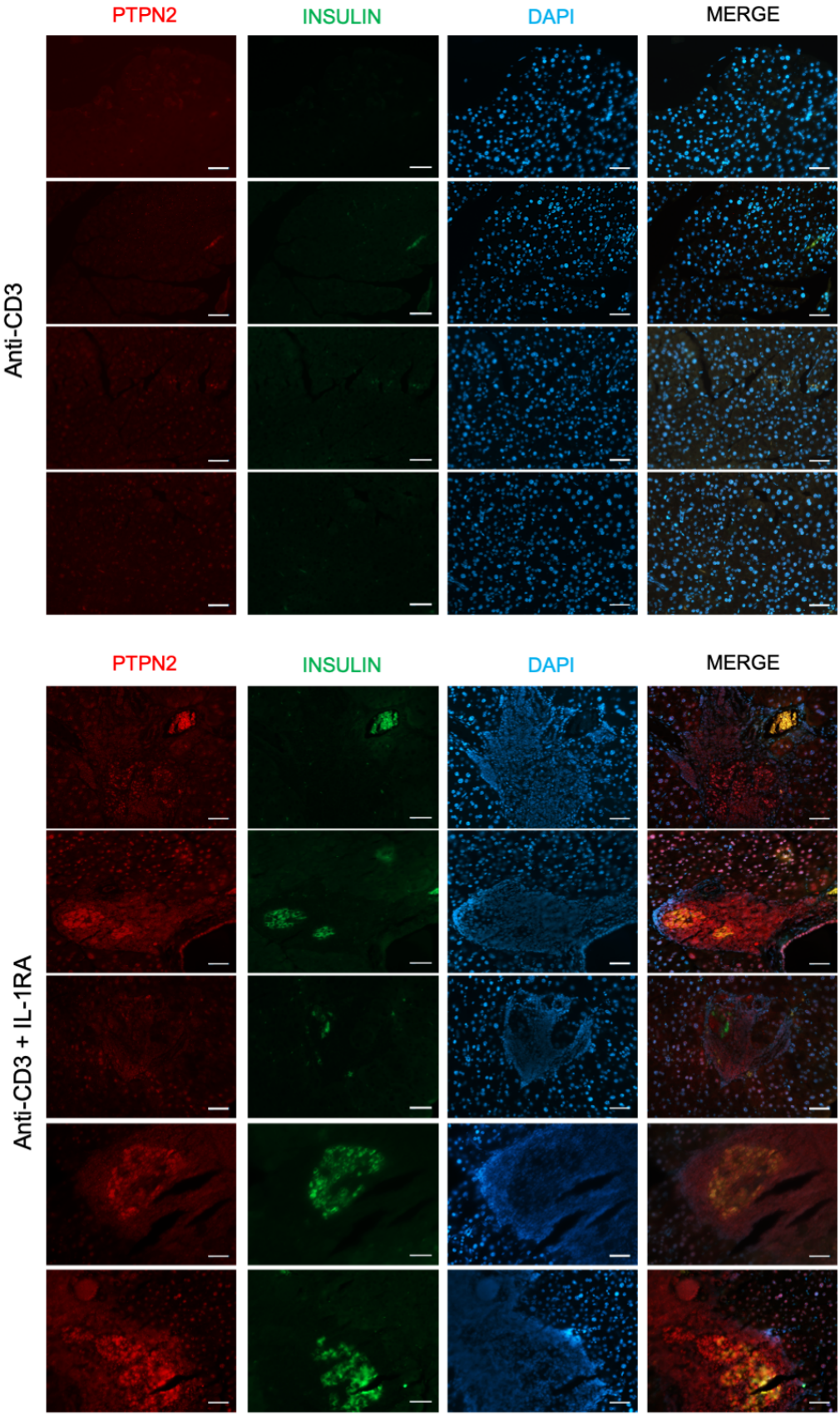



C

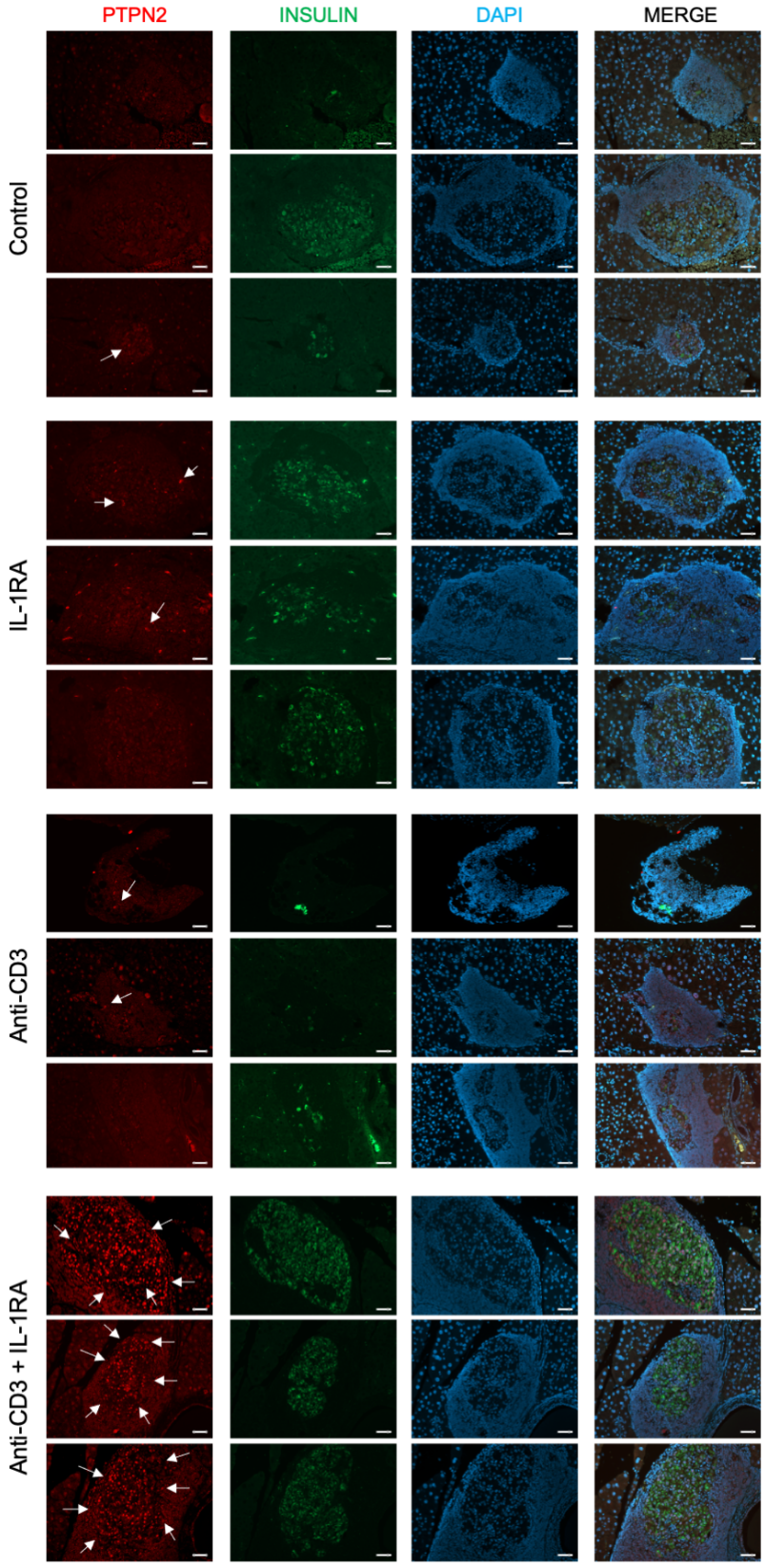
By summed spectra from 3 injection replicates

| Uniprot Accession | Protein name | Gene names | Anti-CD3 #1 | Anti-CD3 #2 | Anti-CD3 #3 | Anti-CD3 + IL1-RA #1 | Anti-CD3 + IL-1RA #2 | Anti-CD3 + IL1-RA #3 | Anti-CD3 + IL-1RA #4 | Anti-CD3 + IL-1RA #5 | Peptide sequence 1 | Peptide sequence 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Q3TU63 | Receptor-type tyrosine-protein phosphatase epsilon | Ptpre | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 2 | TLNPSHAGPIVVHCSAGVGR | |
| A0A1W2P706 | Receptor-type tyrosine-protein phosphatase kappa | Ptprk | 0 | 2 | 4 | 2 | 3 | 2 | 4 | 6 | LSNPPSAGPIVVHCSAGAGR | |
| Q3TS01 | Receptor-type tyrosine-protein phosphatase beta | Ptprb | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | SPGAGPTVVHCSAGVGR | |
| Q3TT24 | Receptor-type tyrosine-protein phosphatase F | Ptprf | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | EQFGQDGPITVHCSAGVGR | |
| Q3UND4 | Receptor-type tyrosine-protein phosphatase gamma | Ptprg | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | MPDMGPVLVHCSAGVGR | |
| Q8C6Q7 | Receptor-type tyrosine-protein phosphatase C | Ptprc | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | VNAFSNFFSGPIVVHCSAGVGR | |
| Q91V35 | Receptor-type tyrosine-protein phosphatase alpha | Ptpra | 0 | 0 | 0 | 1 | 1 | 0 | 5 | 9 | ACNPQYAGAIVVHCSAGVGR | QQQQSGNHPITVHCSAGAGR |
| Q3V3S2 | Receptor-type tyrosine-protein phosphatase mu | Ptprm | 0 | 2 | 2 | 1 | 0 | 0 | 1 | 6 | SPPNAGPLVVHCSAGAGR | |
| Q3UB72 | Tyrosine-protein phosphatase non-receptor type 6 | Ptpn6 | 2 | 4 | 2 | 3 | 4 | 3 | 4 | 6 | QESLPHAGPIIVHCSAGIGR | |
| P35235 | Tyrosine-protein phosphatase non-receptor type 11 | Ptpn11 | 6 | 6 | 8 | 10 | 10 | 9 | 8 | 9 | QESIVDAGPVVVHCSAGIGR | |
| Q3T9Y9 | Tyrosine-protein phosphatase non-receptor type 1 | Ptpn1 | 2 | 2 | 3 | 4 | 3 | 3 | 4 | 3 | ESGSLSLEHGPIVVHCSAGIGR | |
| P35831 | Tyrosine-protein phosphatase non-receptor type 12 | Ptpn12 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | YQEHEDVPICIHCSAGCGR | |
| Q9WU22 | Tyrosine-protein phosphatase non-receptor type 4 | Ptpn4 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 1 | EEPIIVHCSAGIGR | |
| Q3TPD6 | Tyrosine-protein phosphatase non-receptor type 13 | Ptpn13 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 5 | SGPVITHCSAGIGR | |
| A2ALK8 | Tyrosine-protein phosphatase non-receptor type 3 | Ptpn3 | 1 | 2 | 1 | 2 | 0 | 1 | 1 | 0 | VDGEPALVHCSAGIGR | |
| D3Z6W2 | Tyrosine-protein phosphatase non-receptor type 2 | Ptpn2 | 0 | 0 | 0 | 4 | 3 | 3 | 5 | 2 | ESGCLTPDHGPAVIHCSAGIGR | |
| Q2M4G8 | Tyrosine-protein phosphatase non-receptor type 9 | Ptpn9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | GQCPEPPIVVHCSAGIGR | |
| | | PSM total | 14 | 22 | 29 | 30 | 27 | 26 | 37 | 60 | | |

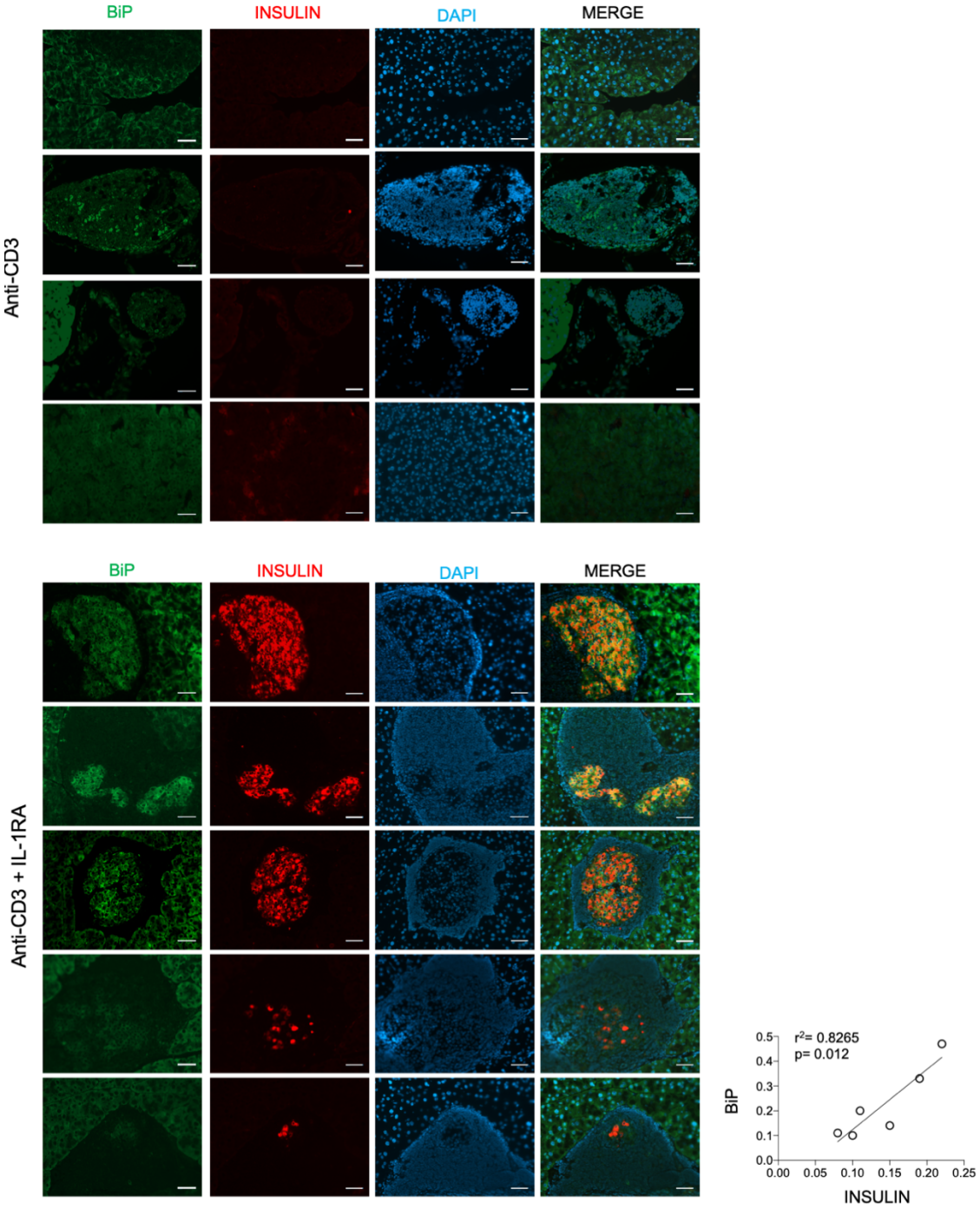
**Supplementary Figure S1. Combined treatment of anti-CD3 and IL-1 receptor antagonist (IL-1RA) cured NOD mice. (A)** Protocol scheme to study the global proteomics and PTP profile from murine pancreas samples. **(B)** Protein profile of pancreata was examined by mass spectrometry. Protein expression of eukaryotic initiator factors and oxidative stress-related proteins is shown. LFQ: label-free quantification. n=5. **(C)** Spectral counts of oxPTP peptides in anti-CD3 + IL-1RA-treated or anti-CD3 control NOD mice. PSM: peptide-spectrum match. *p<0.05, **p<0.01.



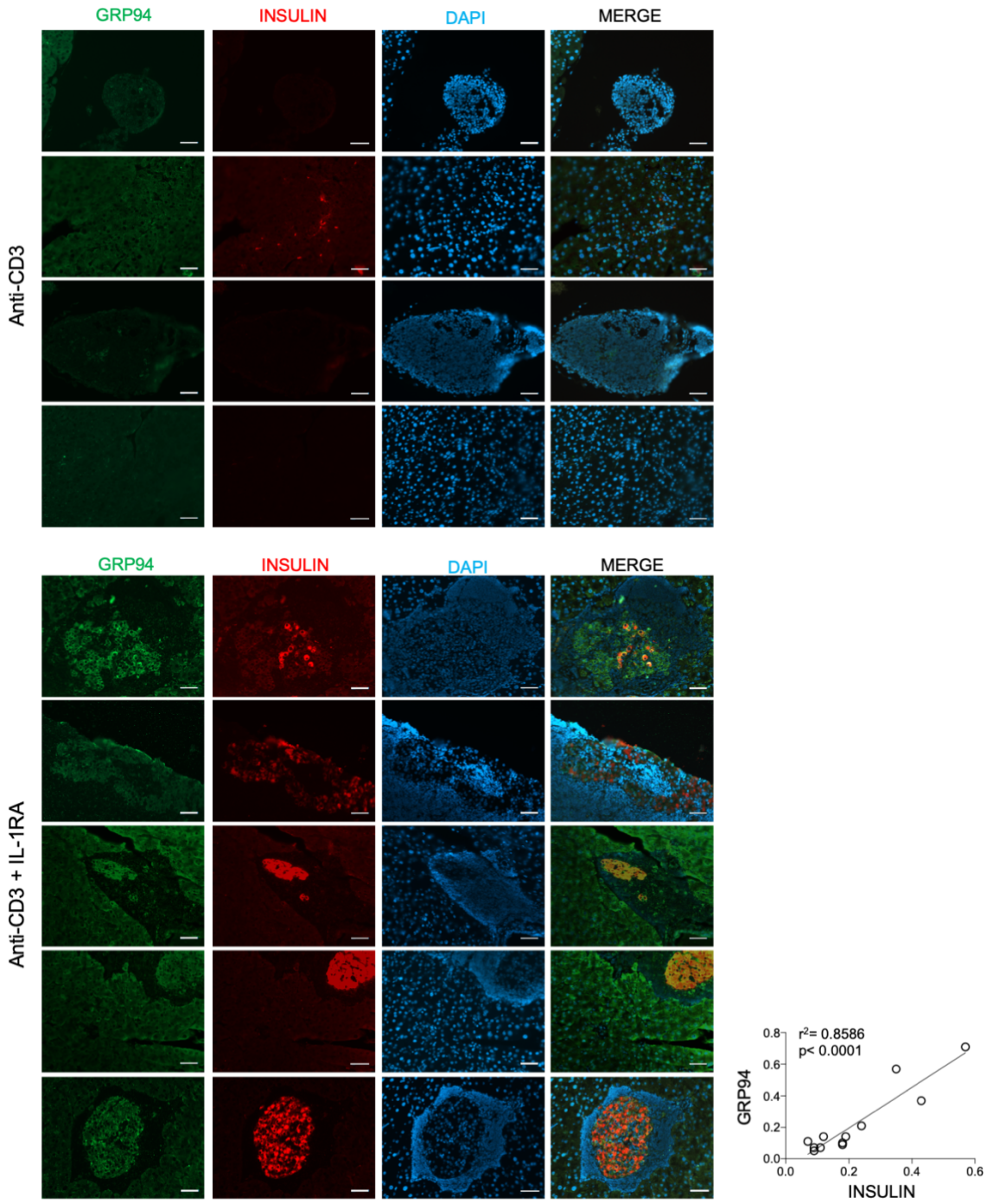

**Supplementary Figure S2. Increased PTPN2 expression in mice with combined treatment of anti-CD3 + IL-1 receptor antagonist (IL-1RA).** Immunofluorescence analysis of insulin and PTPN2 in pancreas sections derived from mice with anti-CD3 antibody + IL-1RA or controls. The nuclei were visualized with DAPI. Scale bar: 50µm.



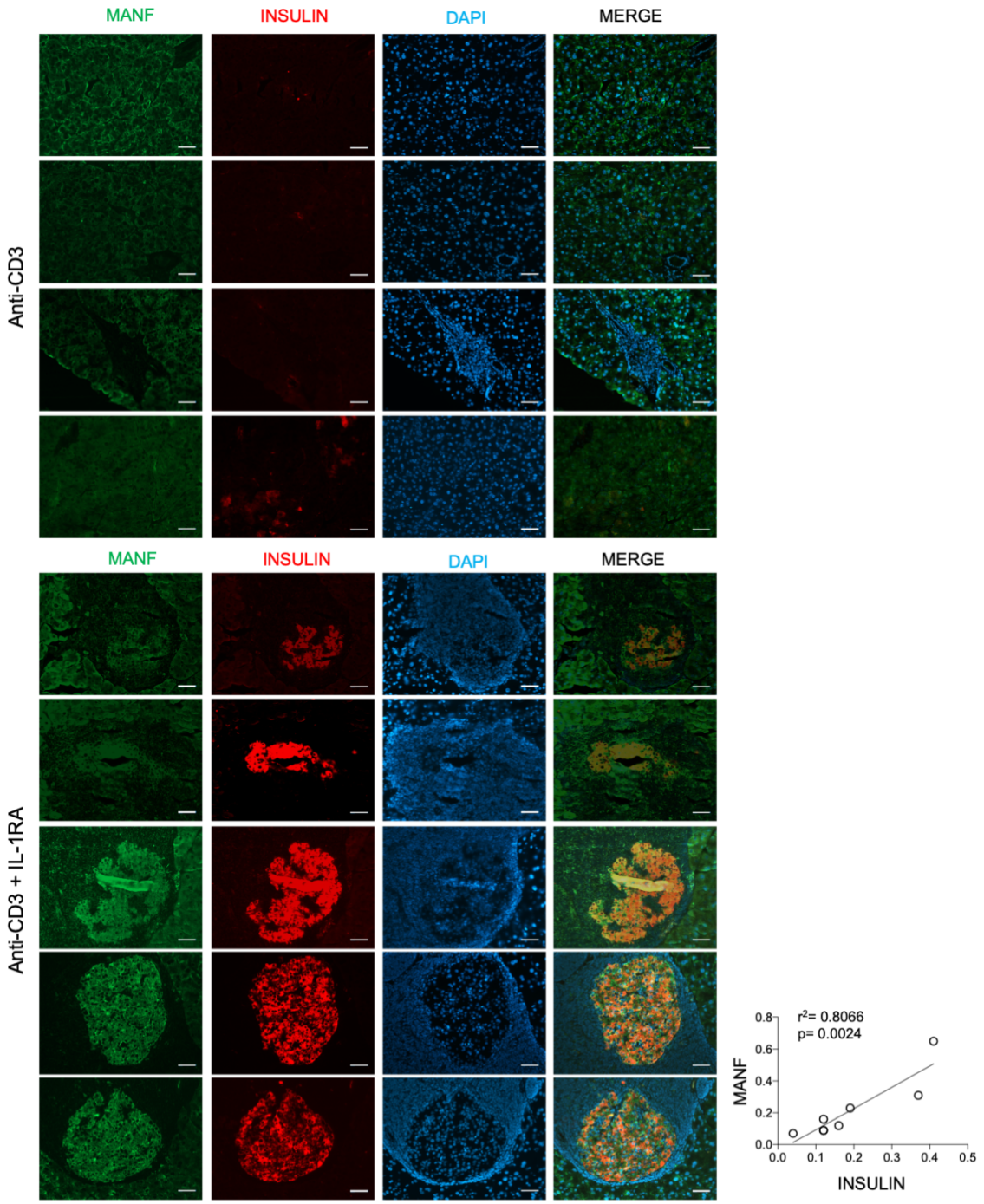

**Supplementary Figure S3. High PTPN2 expression in islets from mice with anti-CD3 + IL-1 receptor antagonist (IL-1RA).** Immunofluorescence analysis of insulin and PTPN2 in pancreas sections derived from mice without treatment (control), IL-1RA, anti-CD3 antibody, or anti-CD3 antibody + IL-1RA. The nuclei were visualized with DAPI. PTPN2 expression in insulin positive cells is shown (white arrows). Scale bar: 50µm.



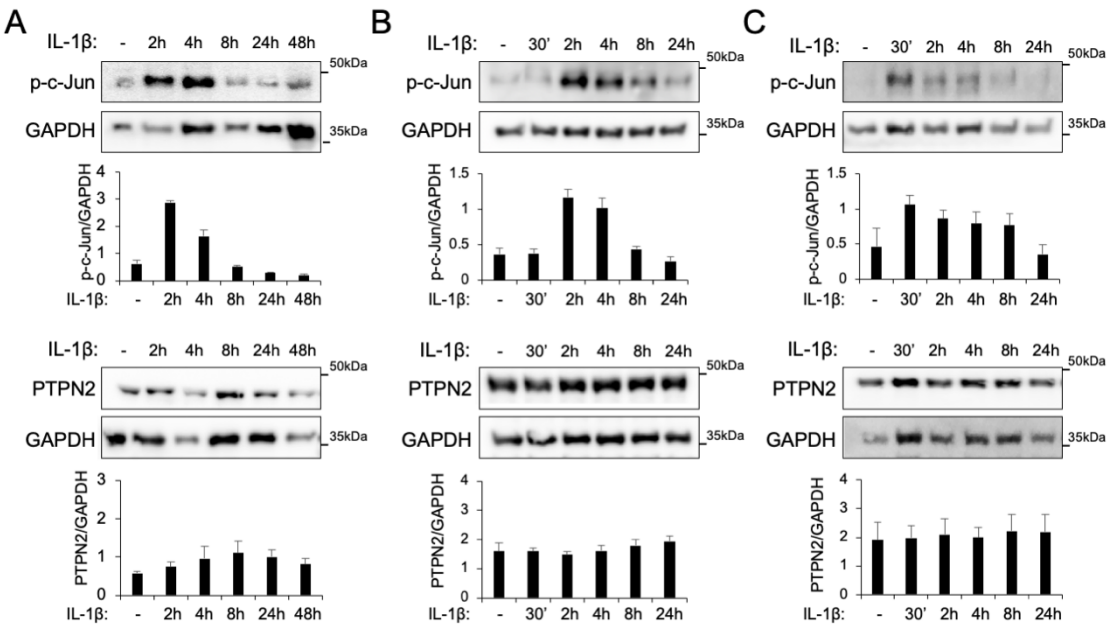

**Supplementary Figure S4. Increased BiP expression in mice with combined treatment of anti-CD3 + IL-1 receptor antagonist (IL-1RA).** Immunofluorescence analysis of insulin and ER stress response-related protein BiP in pancreas sections derived from mice with anti-CD3 + IL-1RA or controls. The nuclei were visualized with DAPI. Scale bar: 50µm. Insulin and GRP94 correlation in pancreatic islets from anti-CD3 + IL-1RA treatment is shown.



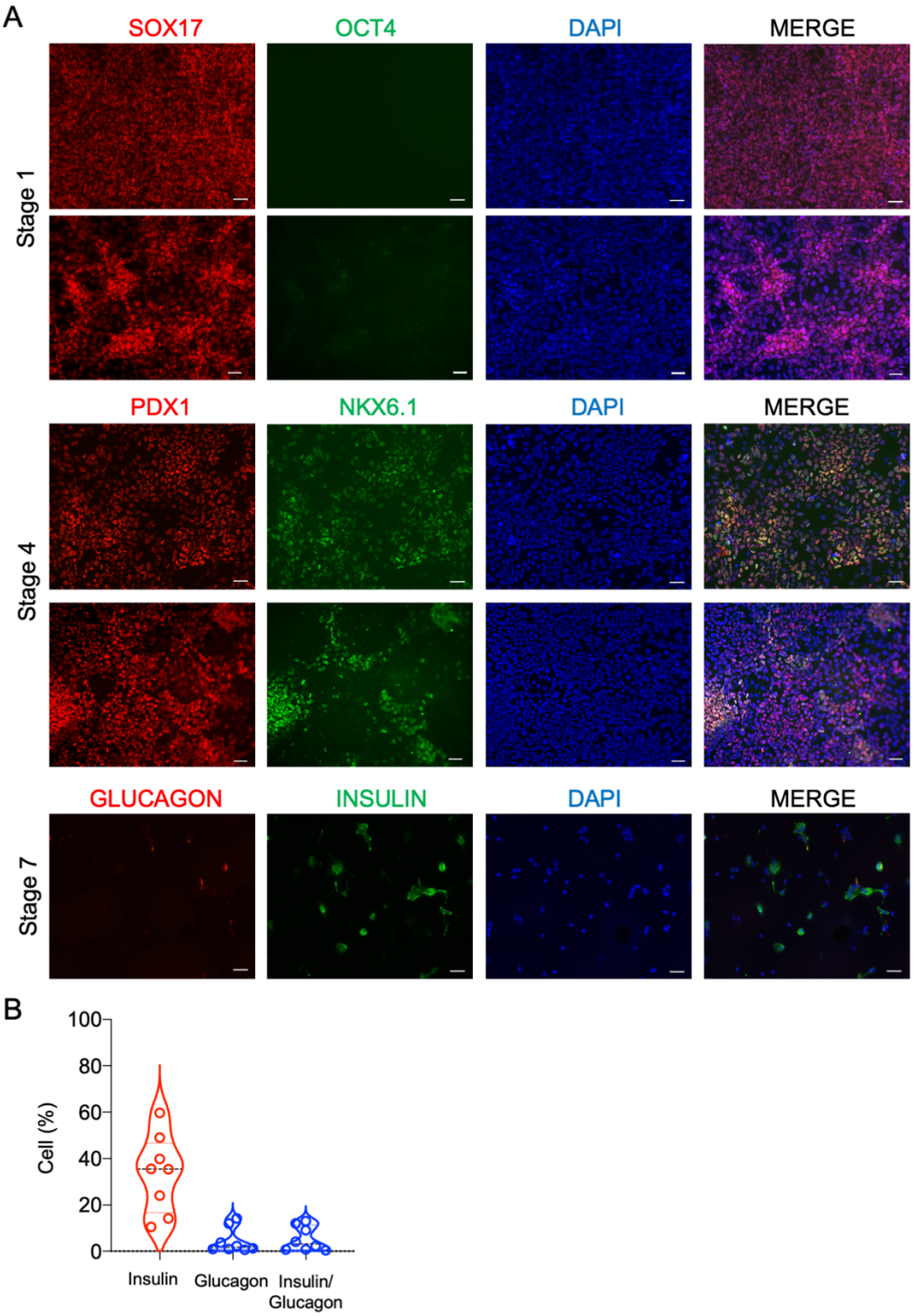

**Supplementary Figure S5. Increased GRP94 expression in mice with combined treatment of anti-CD3 + IL-1 receptor antagonist (IL-1RA)**. Immunofluorescence analysis of insulin and ER stress response-related protein GRP94 in pancreas sections derived from mice with anti-CD3 + IL-1RA or controls. The nuclei were visualized with DAPI. Scale bar: 50µm. Insulin and GRP94 correlation in pancreatic islets from anti-CD3 + IL-1RA treatment is shown.



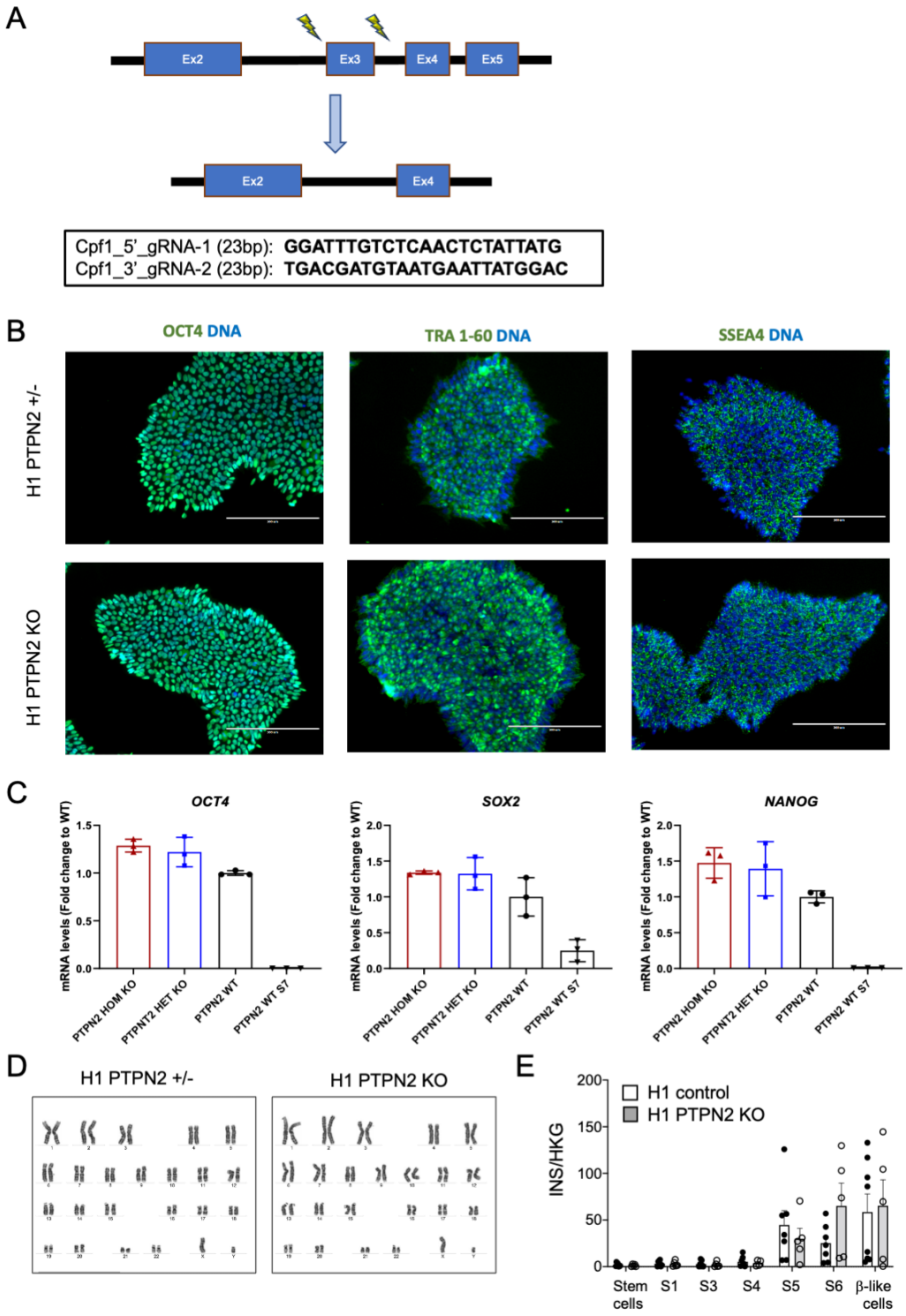

**Supplementary Figure S6. Increased MANF expression in mice with combined treatment of anti-CD3 + IL-1 receptor antagonist (IL1RA).** Immunofluorescence analysis of insulin and ER stress response-related protein MANF in pancreas sections derived from mice with anti-CD3 + IL-1RA or controls. The nuclei were visualized with DAPI. Scale bar: 50µm. Insulin and MANF correlation in pancreatic islets from anti-CD3 + IL-1RA treatment is shown.



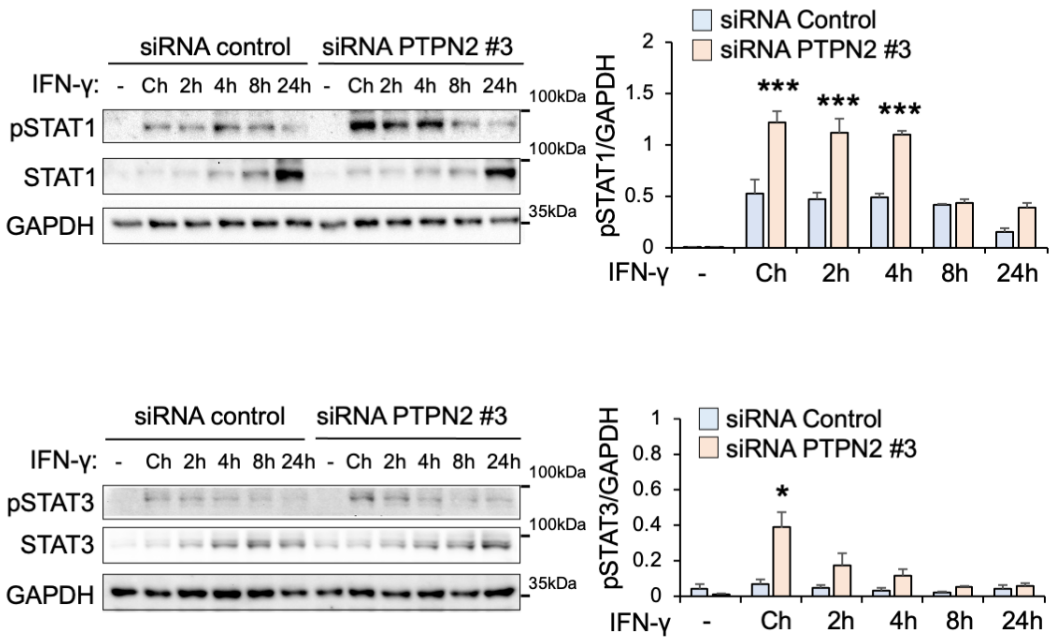

**Supplementary Figure S7. IL-1β does not modulate PTPN2 in isles/β-cells. (A)** C57BL/6 mouse islets were isolated and treated with IL-1β (50U/ml) as indicated. p-c-Jun (activated by IL-1β), PTPN2 and GAPDH were assessed by Western blot. n=2. **(B)** EndoC-βH1 cells were treated with IL-1β (50U/ml) as indicated. p-c-Jun (activated by IL-1β), PTPN2 and GAPDH were assessed by Western blot. n=4. **(C)** H1-differentiated β-like cells were treated with IL-1β (50U/ml) as indicated. p-c-Jun (activated by IL-1β), PTPN2 and GAPDH were assessed by Western blot. n=3.



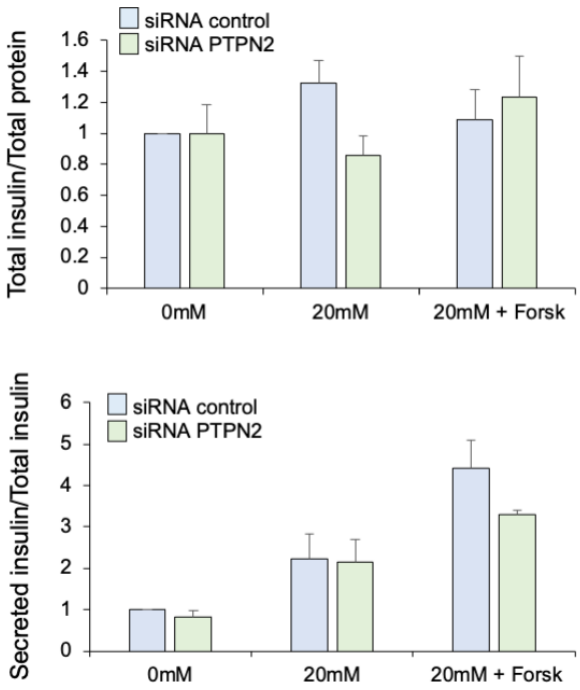

**Supplementary Figure S8. Characterisation of stem cell differentiation. (A)** Immunofluorescence staining of Hel46.11 hiPSC differentiation markers in the different stages as indicated. 2 independent differentiations are represented. **(B)** Percentage of insulin, glucagon and insulin/glucagon double-positive cells by immunofluorescence in insulin-producing Hel46.11 and H1 differentiated cells. The results are expressed as percentage of total cell number. n=8.



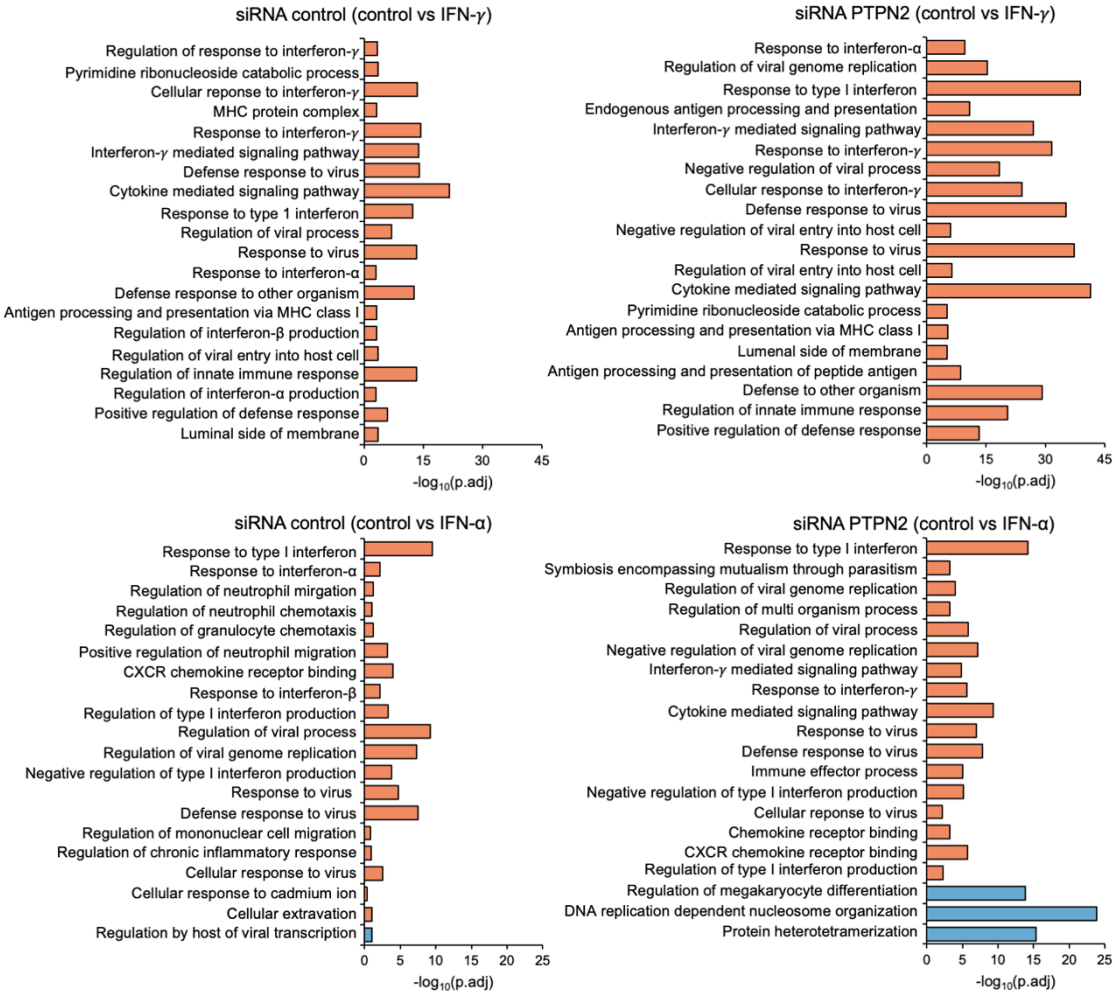

**Supplementary Figure S9. Characterization of H1 cell lines with *PTPN2* gene editing using CRISPR/Cpf1. (A)** Scheme of *PTPN2* exon 3 deletion. **(B)** Immunofluorescence staining of pluripotency markers (OCT4, TRA1-60 and SSEA4) in undifferentiated H1 cells. Scale bar: 200µm. **(C)** OCT4, SOX2 and NANOG mRNA expression assessed by real-time PCR in undifferentiated H1 cell lines and the stage 7 (S7) of H1 wild-type cell line. Results were normalised with PPIG as internal housekeeping control gene. n=3. **(D)** Karyotype of H1 wild-type and H1 homozygous knockout. **(E)** Insulin mRNA expression assessed by real-time PCR during the 7 stages of H1 cells differentiation into β-like cells. Results were normalized with mean of GAPDH and β-actin as internal housekeeping genes. n=5-8.



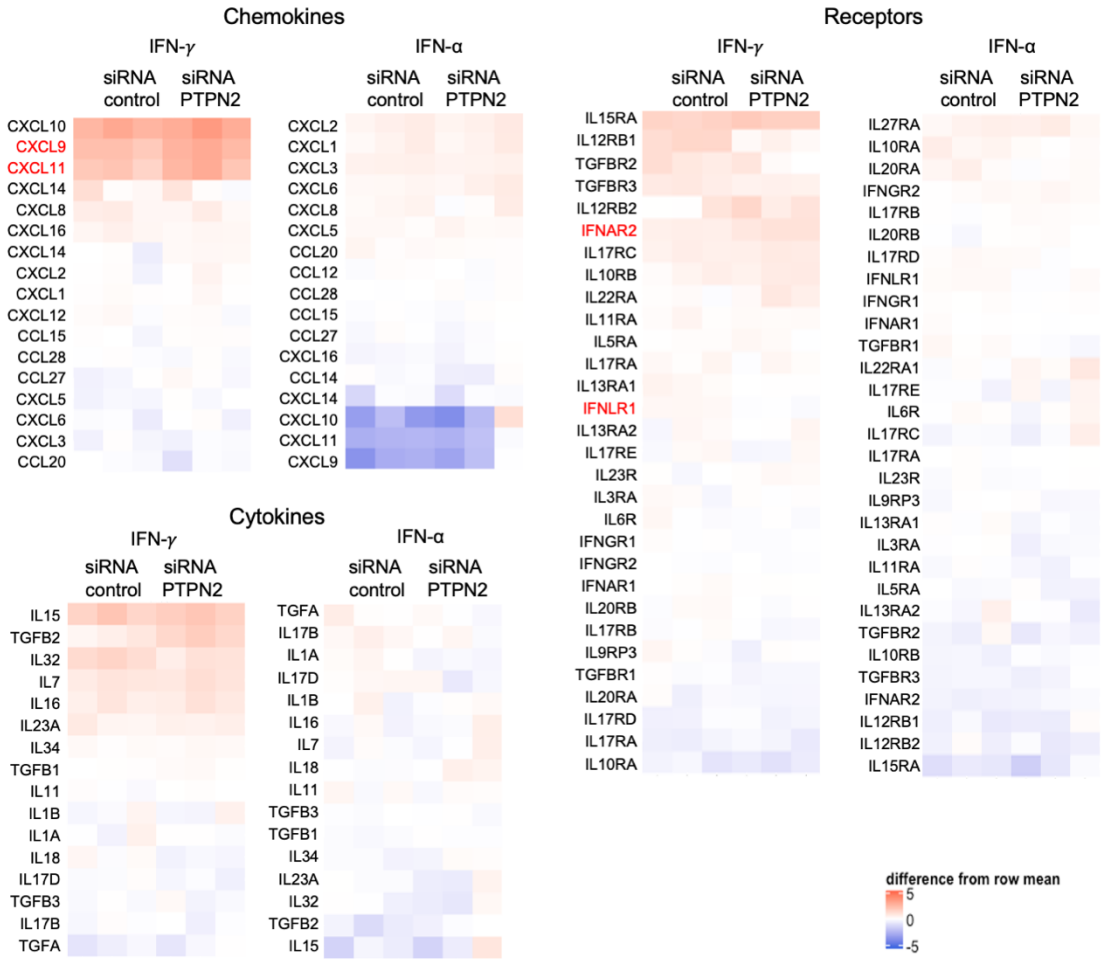

**Supplementary Figure S10. PTPN2 regulates STAT1 and STAT3 phosphorylation in IFN-γ-treated β-cells.** Transfected EndoC-βH1 cells with control or PTPN2 (#3) siRNA were cultured with the pro-inflammatory cytokine IFN-γ for 1h in a pulse-chase experiment. Western blot for pSTAT1, total STAT1, pSTAT3, total STAT3 and GAPDH was performed. Error bars represent ± SEM. N=4. *p<0.05, ***p<0.001.



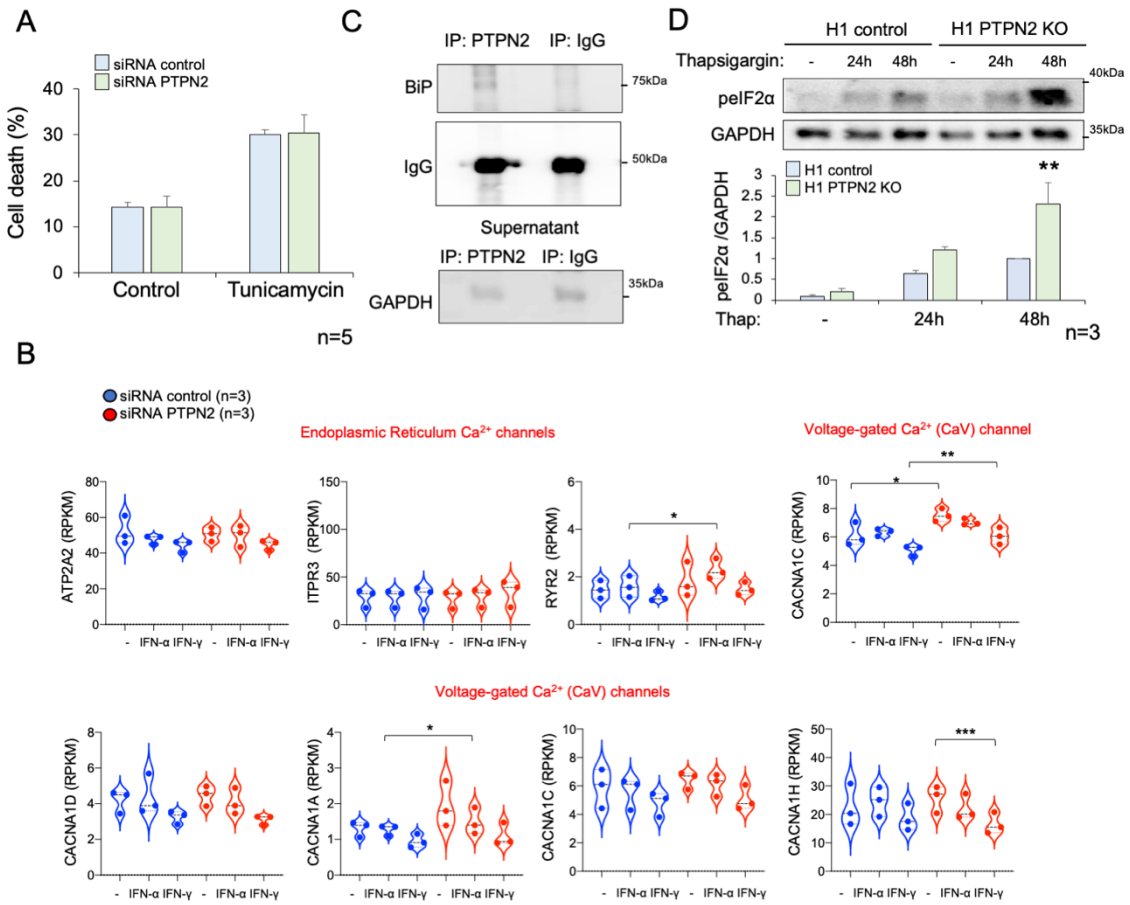

**Supplementary Figure S11. PTPN2 deficiency does not affect glucose-induced insulin secretion in EndoC-βH1 cells.** Total and secreted insulin analysis between siRNA PTPN2 or control transfected EndoC-βH1 cells without glucose, exposed to high glucose (20mM) or high glucose and forskolin (10µM, Sigma-Aldrich). Insulin was measure with an ELISA kit (Mercodia, NC, USA)**.** n=5.



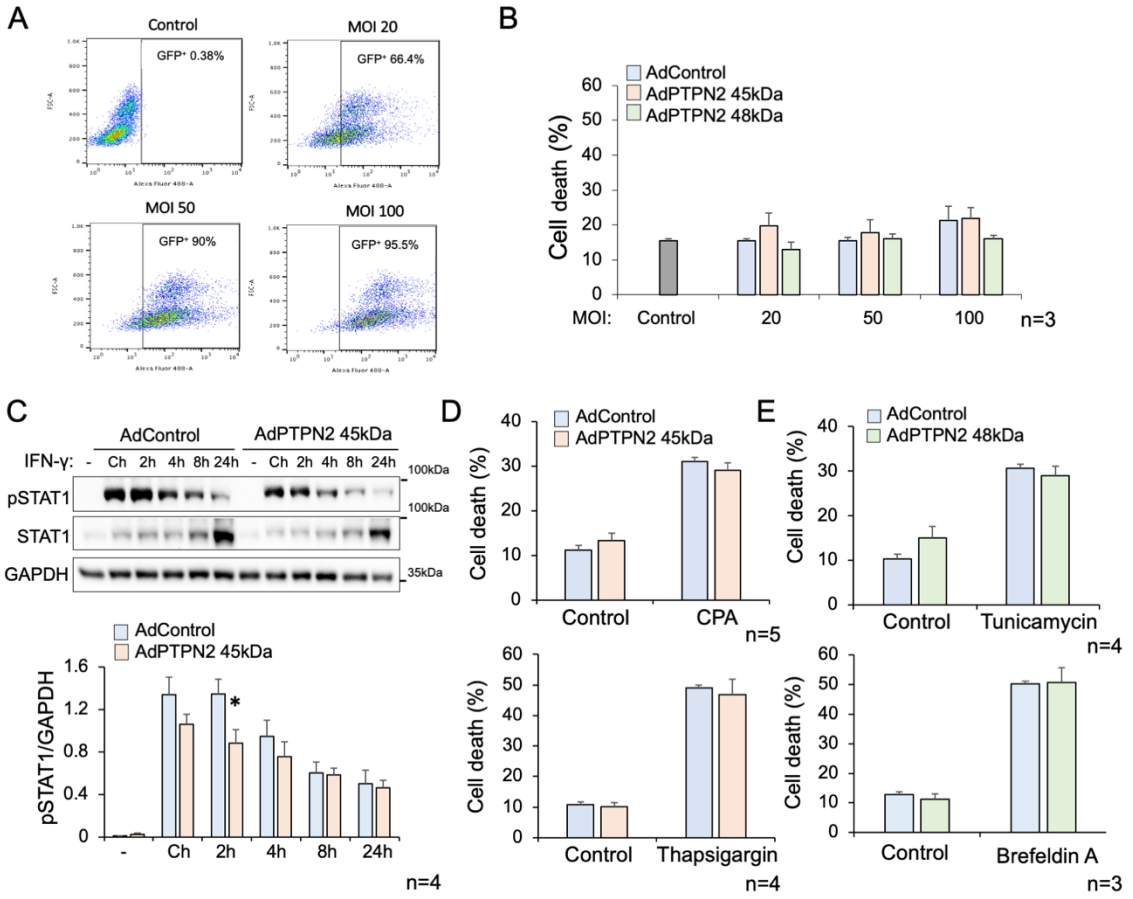

**Supplementary Figure S12. PTPN2 regulates immune response pathways after cytokine treatment in β-cells.** Pathway enrichment analysis of the comparison between siRNA PTPN2 or control transfected EndoC-βH1 cells and treated with IFN-γ or IFN-α. The length of the bars is proportional to the level of significant change, expressed by the negative logarithm of the adjusted p-value. Orange upregulated and blue downregulated pathways with $p < 0.05$ are shown**.**




**Supplementary Figure S13. Chemokines, cytokines and receptor expression in interferon-treated PTPN2 deficiency β-cells.** Heatmap analysis of siRNA PTPN2 or control transfected EndoC-βH1 cells obtained by RNA-Seq. The counts are scaled to the difference of the row mean. Gene expression is considered significant upon an FDR<0.05 (showed in red). n=3.




**Supplementary Figure S14. The role of PTPN2 deficiency in β-cell death and $Ca^{2+}$ channel expression. (A)** Transfected cells with PTPN2 or control siRNAs were cultured with tunicamycin for 48h. β-cell apoptosis was evaluated by Hoechst 33342/propidium iodide staining. n=5. **(B)** Gene counts obtained by RNA-Seq were normalised to reads per kilobase million (RPKM) using Rstudio. n=3. **(C)** PTPN2 and control (IgG) immunoprecipitation of EndoC-βH1 cells transduced with AdPTPN2 48kDa. BiP binding was detected by Western blot analysis in the pull down. GAPDH levels in the supernatant is used as sample loading. The result is representative of 2 independent experiments. **(D)** Dispersed H1-derived β-like cells were cultured with thapsigargin for 24 or 48h as indicated. Protein expression of ER stress marker peIF2α was examined by Western blot. n=3. *p<0.05, **p<0.01, ***p<0.001.




**Supplementary Figure S15. Characterization of ER stress modulation by different PTPN2 isoforms. (A-B)** EndoC-βH1 cells were transduced with AdControl, AdPTPN2 45kDa or AdPTPN2 48kDa. **(A)** Transduction efficiency counting GFP positive cells was measured by flow cytometry. **(B)** β-cell apoptosis was evaluated by Zombie Aqua™ staining and flow cytometry. n=3. **(C)** Transduced cells with AdPTPN2 45kDa or AdControl were cultured with the pro-inflammatory cytokine IFN-γ for 1h in a pulse-chase experiment. Western blot for pSTAT1, total STAT1. n=4. **(D)** Transduced cells with AdPTPN2 45kDa or AdControl were cultured either with CPA or with thapsigargin for 48h. β-cell apoptosis was evaluated by Hoechst 33342/propidium iodide staining. n=4-5. (**E)** Transduced cells with AdPTPN2 48kDa or AdControl were cultured either with tunicamycin for 48h or with brefeldin A for 24h. β-cell death was evaluated by Hoechst 33342/propidium iodide staining. n=3-4. *p<0.05.