SUPPLEMENTARY DATA

Supplementary Table S1. Characteristics of the organ donors and human islet preparations used.

ID	Gender	Age (years)	BMI (kg/m^2)	Cause of death	Purity (%)
ID1	M	69	25	CVD	85
ID2	M	85	25.5	CH	39
ID3	M	59	27.7	TR	56
ID4	F	76	19.5	CH	35
ID5	F	64	23.4	CH	76
ID6	M	42	32.6	TR	36
ID7	M	78	23.4	TR	43
ID8	F	63	27.3	ST	58
ID9	F	63	26	CH	45

The abbreviations used are as follows: F, female; M, male; BMI, body mass index; CVD, cardiovascular disease; CH, cerebral hemorrhage; TR, trauma; ST, stroke. Purity indicates the percentage of beta cells in the human islet preparations as determined by immunostaining for insulin.

Supplementary Table S2. Sequences of siRNAs used to knock down gene expression.

Name	Supplier	Sequence
siCTL (Allstars Negative Control siRNA)	Qiagen, Venlo, Netherlands	Not provided
siSRp55#1 Silencer Select siRNAi	Invitrogen, Pasley, UK	5'GCGUCUACAUAGGACGCCUGAGCUA 3'
siSRp55#2 Silencer Select siRNAi	Invitrogen, Pasley, UK	5'CCUGUUCGUACAGAAUACAGGCUUA3'
siBAXβ Custom designed	Dharmacon, Lafayette, USA	Sense 5' UCGCUAUGUUGCCCAGGUUUU 3' Antisense 5' AACCUGGGCAACAUAGCGAUU 3'
siBIM Silencer Select siRNAi	Invitrogen, Pasley, UK	5' ACGAAUGGUUAUCUUACGACUGUU 3'
siJNK1 Silencer Select siRNAi	Invitrogen, Pasley, UK	5'GGGCCUACAGAGAGCUAGUUCUUAU3'
siIRE1α Silencer Select siRNAi	Invitrogen, Pasley, UK	5'CCCUACCUACACGGUGGACAUCUUU 3'
siMAP3K7e12 Custom designed	Dharmacon	Sense 5' UGGAUGUCCCUGAGAUCGUUU 3' Antisense 5' ACGAUCUCAGGGACAUCCAUU 3'
siJNK1e3 Custom designed	Dharmacon	Sense 5' UCACAGAGGUAAAGCAUCAUU 3' Antisense 5' UGAUGCUUUACCUCUGUGAUU 3'
siJNK2e2 Custom designed	Lafayette, USA	Sense 5' AGUCUGACCCUGAACGUUAUU 3' Antisense 5' UAACGUUCAGGGUCAGACUUU 3'

SUPPLEMENTARY DATA

Supplementary Table S3. Sequences of primers used for splicing analyses and real time.

Gene Target	Application	Forward (5'-3')	Reverse (5'-3')
BAX	SPL	AGCAAACTGGTGCTCAAGG	CGTCCCAAAGTAGGAGAGGA CACTGTGACCTGCTCCAGAA
BIM	SPL	ATGGCAAAGCAACCTTCTG	CTCCTTGCATAGTAAGCGT
SMARCC2	SPL	CGACTGAACCCCCAAGAGTA	CCTGTTCTGTCCACTCACGA
DNM2	SPL	CCCCGGACTTGGCATTCGAG TCTTCACCCCCGACATGGCC	CTGGTACACTGCCTAACTG ACCGTGGCCAGCTCTGAGACCA
SNAP25	SPL	CGTGTCGAAGAAGGCATGAACC GAACAAGGAGAACAACTGG	GACATATGAAAAGGCCACAGC GCTTGTTACAGGGACACACAC
CACNA2D1	SPL	GTGTGATGGGAGTAGATGTGTC	CATTCTCTAACTCTGCATC
CACNA1D	SPL	GCCTCAGAGAAGGTCCAGTG	AGTGGGGGTCCCTGAAATAG
MAPK9 (JNK2)	SPL	GCAAGTGGCAGACTCAACCT	TTTGTGGTGTAAACACATTTAACAAA
MAP3K7	SPL	GTGGGAGCAGTGTGGAGAG	TGACCAGGTTCTGTTCCAGTT
MAPK8 (JNK1)	SPL	CGGCTTCTTGGTGAATTTTT CGGTCTTGCAGCCTTACAGT	CCTTGAGCTCCTGAGCCTAT
DIABLO	SPL	GGCTCTGAAGAGTTGGCTGT	CCTCTGAATTCATTTTCCCAAG
INSR	SPL	TGAGGATTACCTGCACAACG	GAGGAAGTGTTGGGGAAAGC
ACTB	qRT	CTGTACGCCAACACAGTGCT	GCTCAGGAGGAGCAATGATC
SRSF6 (SRp55)	qRT	CATAGGACGCCTGAGCTACA	TGCCGTTCAGCTCGTAAAC
FOXO1	qRT	CGTGCCCTACTTCAAGGATAA	CACGAATGAACTTGCTGTGTAG
NEUROD1	qRT	CTATCACTGCTCAGGACCTACT	CCACTCTCGCTGTACGATTT
NKX6.1	qRT	GGGCTCGTTTGGCCTATT	CGTGCTTCTTCCTCCACTT
PDX1	qRT	AAAGCTCACGCGTGGAAA	GCCGTGAGATGTACTTGTTGA
BIM	qRT	TTCTTGCAGCCACCCTGC	CTTGCGTTTCTCAGTCCGA
BIM S	qRT	GAGCCACAAGCTTCCATGAG	TAACCATTCGTGGGTGGTCT
BAXβ	qRT	AGGGTGGTTGGGTGAGACT	AGGGTCCCAGAGGAGTGG
MAPK8	qRT	GGACTGCAGGAACGAGTTTT	CAACTGACCAAATGTCAACG
CHOP	qRT	QuantiTect QT00082278	QuantiTect QT00082278
BIP	qRT	QuantiTect QT00096404	QuantiTect QT00096404
XBP1 spliced	qRT	CCGCAGCAGGTGCAGG	GAGTCAATACCGCCAGAATCCA
ERN1 (IRE1α)	qRT	GGGCGAACAGAATACACCAT	GGCCGCATAGTCAAAGTAGG

The abbreviations used are as follows: SPL, primers used to analyse splicing variants; qRT, primers used for real time qRT-PCR;

SUPPLEMENTARY DATA

Supplementary Table S4. Antibodies used for Western blotting and immunofluorescence are listed.

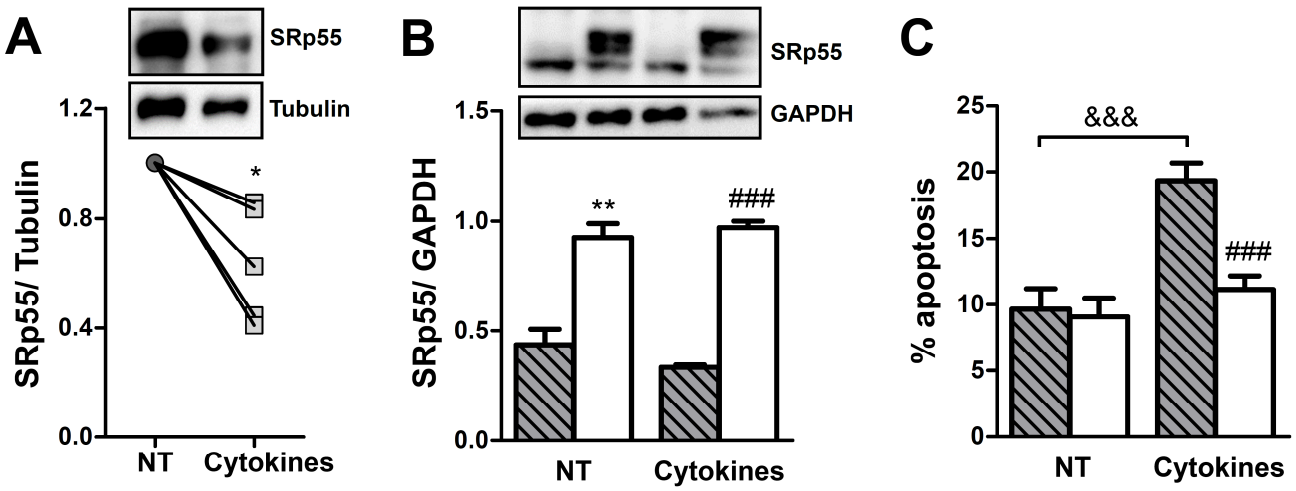
Antibodies	Source	Identifier	Dilution
Insulin (mouse)	Sigma-Aldrich, Bornem, Belgium	I2018	IHC: 1:500
SRSF6/ SRp55 (rabbit)	LifeSpan Bioscience	LS-B5712	IHC: 1:500
SRSF6/ SRp55 (rabbit)	LifeSpan Bioscience	LS-C290327	WB: 1:1000
SAPK/JNK (mouse)	Cell Signaling Technology	9251S	WB: 1:1000
JNK1 (mouse)	Cell Signaling Technology	3708S	WB: 1:1000
Phospho-JNK (rabbit)	Cell Signaling Technology	#9251	WB: 1:1000
MKK7 (rabbit)	Cell Signaling Technology	#4172	WB: 1:1000
Phospho-MKK7 (rabbit)	Merck Millipore	36-013	WB: 1:1000
c-JUN (rabbit)	Cell Signaling Technology	#9165	WB: 1:1000
Phospho-c-JUN (rabbit)	Cell Signaling Technology	#9164	WB: 1:1000
eIF2α (rabbit)	Cell Signaling Technology	#5324	WB: 1:1000
Phospho-eIF2α (rabbit)	Cell Signaling Technology	#3597	WB: 1:1000
PERK (rabbit)	Cell Signaling Technology	#3192	WB: 1:1000
Phospho-PERK (rabbit)	Cell Signaling Technology	#3179	WB: 1:1000
Phospho-IRE1α (rabbit)	Novusbio, Littleton, USA	NB100-2323	WB: 1:500
IRE1α (rabbit)	Cell Signaling Technology	#3294	WB: 1:1000
ATF3 (rabbit)	Santa Cruz Biotechnology	sc188	WB: 1:1000
Cleaved Caspase 3 (rabbit)	Cell Signaling Technology	#9664	ICC: 1:200
BAX (rabbit)	Santa Cruz Biotechnology	sc-492	ICC: 1:200
ATP synthase β (mouse)	Sigma-Aldrich, Bornem, Belgium	A9728	ICC: 1:500
BIM (rabbit)	Cell Signaling Technology	#2819	WB: 1:1000
α-Tubulin (mouse)	Sigma Aldrich	T5168	WB: 1:5000
Caspase 3	Cell Signaling Technology	9661S	ICC: 1:200

Supplementary Table S5. Alternative splicing events modified by SRp55 depletion in EndoC-βH1 cells. List of modified cassette exons **(S5.1)**, mutually exclusive exons **(S5.2)**, alternative 3' splice sites **(S5.3)**, alternative 5' splice sites **(S5.4)** and retained introns **(S5.5)**. For each event the genomic coordinates, gene name and difference in PSI (ΔPSI) are indicated. **S5.6)** List of gene ontology (biological process) enriched terms in all alternatively-spliced genes. **S5.7)** List of KEGG enriched pathways in all alternatively-spliced genes.

Supplementary Table S6. Genes modified by SRp55 depletion in EndoC-βH1 cells. S6.1) List of down-regulated genes. Median RPKM expression for each condition and log2 fold change are indicated. **S6.2)** List of gene ontology (biological process) enriched terms in down-regulated genes. **S6.3)** List of KEGG enriched pathways in down-regulated genes. **S6.4)** List of up-regulated genes. Median RPKM expression for each condition and log2 fold change are indicated. **S6.5)** List of gene ontology (biological process) enriched terms in up-regulated genes. **S6.6)** List of KEGG enriched pathways in up-regulated genes.

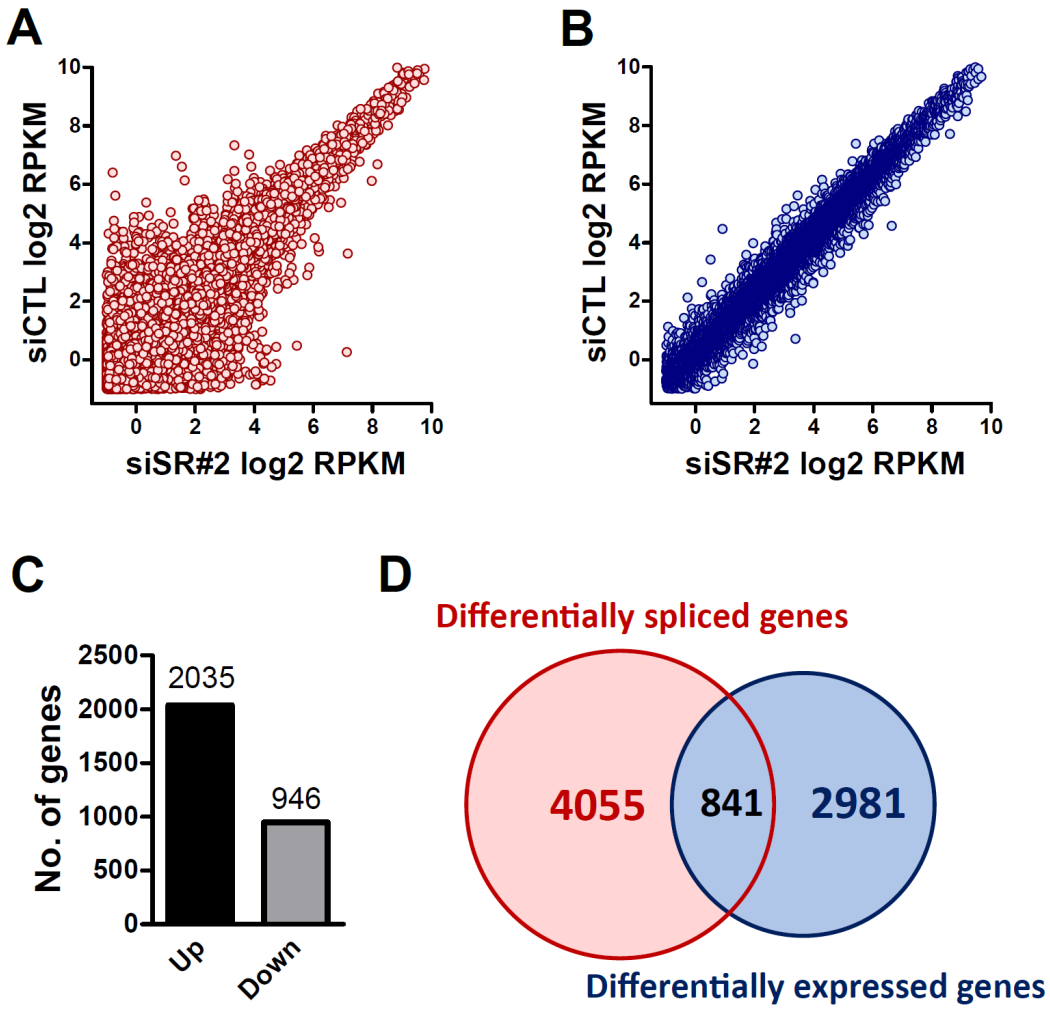
SUPPLEMENTARY DATA

Supplementary Figure 1. SRp55 is down-regulated by pro-inflammatory cytokines and this contributes to cytokine-induced beta cell death. A) Representative western blot and densitometric measurements showing the expression of SRp55 in EndoC-βH1 cells non-treated (NT) or following a 48 h exposure to IL-1β + IFN-γ (cytokines). **B and C)** EndoC-βH1 cells were transfected with an empty vector (pFLAG) or a vector expressing SRp55 (pSRp55). After transfection, cells were left untreated or exposed to IL-1β plus IFN-γ for 48 h. **B)** SRp55 protein expression was evaluated by Western-blot. Expression values were normalized by the highest value of each experiment, considered as 1. **C)** Apoptosis was evaluated by Hoechst/PI staining. Results are mean ± SEM of three to six independent experiments. **A)** *p < 0.05 non-treated (NT) vs cytokines by paired t test. **B and C)** **p < 0.01 pFLAG vs pSRp55 under non-treated conditions, ###p<0.001 pFLAG vs pSRp55 under cytokines exposure, and &&&p<0.001 as indicated by a bar by ANOVA followed by Bonferroni post hoc test.



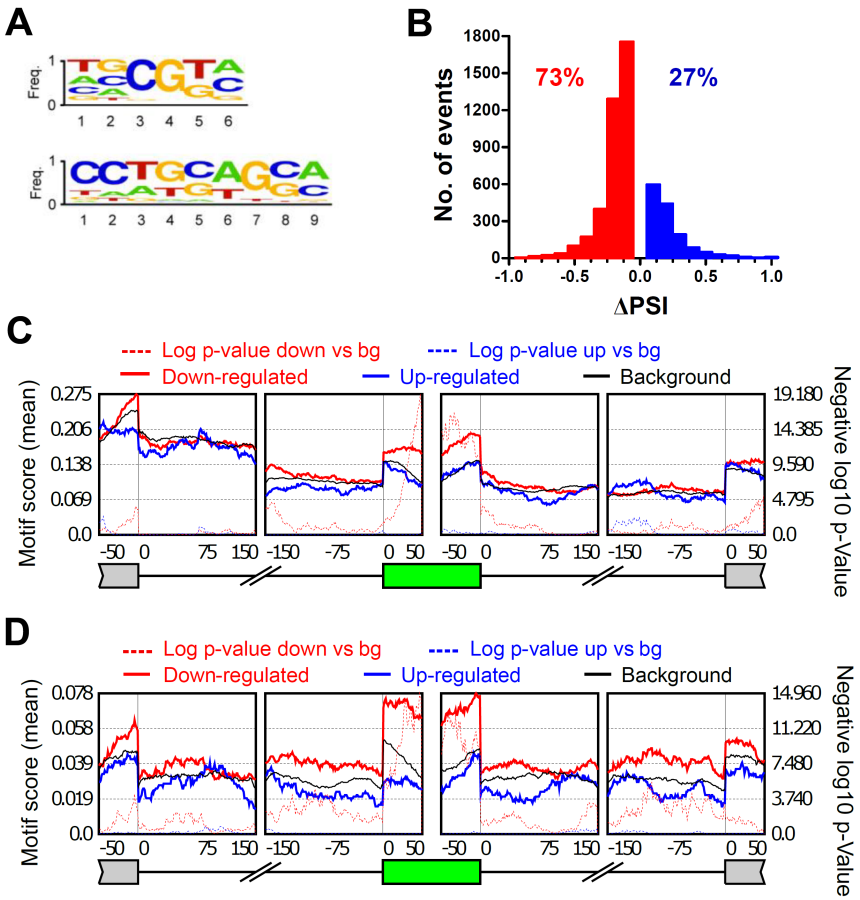
SUPPLEMENTARY DATA

Supplementary Figure 2. Impact of SRp55 depletion on alternative splicing as compared to gene expression. **A)** Expression profiles of splice variants in control versus SRp55-KD cells. **B)** Expression profiles of genes in control versus SRp55-KD cells. **C)** Number of up- and down-regulated genes following SRp55 silencing. **D)** Venn diagram showing the overlap between differentially spliced and differentially expressed genes. Results are based on five independent experiments.



SUPPLEMENTARY DATA

Supplementary Figure 3. Enrichment analysis of SRp55 binding-motifs in modified cassette exons. A) Position weight matrices of SRp55 binding-motifs identified by SELEX (6-mer on the upper side) and by *de novo* prediction after SRp55 overexpression (9-mer on the lower side). **B)** Distribution of ΔPSI values in modified cassette exons, showing a clear predominance of exon skipping. **(C-D)** Representation of the spatial distribution of SRp55 binding-motifs in the vicinity of alternatively spliced cassette exons. The position weigh matrices shown in **(A)** were used to scan the occurrence of binding motifs in respectively 1,449 and 3,820 up-regulated or down-regulated exons whose inclusion is impacted by SRp55 KD, and compared against 134,507 non-modified cassette exons (FDR ≥50%). The solid lines indicate the mean SRp55 binding motif score for each nucleotide position. Doted lines indicate log10 p-values obtained by statistical comparison of motif scores between modified exons (down- or up-regulated) against non-modified background exons, showing significant enrichment of the SRp55 binding motif in exonic sequences of down-regulated exons. The green box represents an average cassette exon, while solid lines and grey boxes represent neighbouring introns and up- and down-stream exons respectively. The numbers shown above indicate the relative nucleotide position from exon-intron junctions. Enrichment of the 6-mer motif is shown in **(C)**, while enrichment of the 9-mer motif is shown in **(D)**. Results are based on five independent RNA-seq experiments.



SUPPLEMENTARY DATA

Supplementary Figure 4. SRp55 KD affects splicing and expression of the pro-apoptotic protein BIM contributing to beta cell apoptosis. A) Representative western blot showing the expression of BIM isoforms in control and SRp55 KD EndoC-βH1 cells. **B)** Ratio between BIM small (S) and BIM large (L) isoforms was calculated by densitometry**. C)** Protein expression of total BIM was measured by densitometry of all BIM isoforms and normalized by α-tubulin as loading control. Protein expression values were normalized by the highest value of each experiment, considered as 1. **D-F)** Double KD of SRp55 and BIM in EndoC-βH1 cells. Cells were transfected with siCTL, siSRp55#2, siBim or siSRp55#2 + siBim for 48 h. mRNA expression of SRp551 **(D)** and BIM S **(E)** was measured by qRT-PCR and normalized by the housekeeping gene β-actin. mRNA expression values were normalized by the highest value of each experiment, considered as 1. **F)** Proportion of apoptotic cells was evaluated by Hoechst/PI staining. Results are mean ± SEM of four to five independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL; ##p < 0.01 and ###p < 0.001 as indicated by bars. **B, C)** Paired t-test. **D-F)** ANOVA followed by Bonferroni post hoc test.