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# **Supplemental information**

## Mining the transcriptome of target tissues

### of autoimmune and degenerative pancreatic $\beta$ -cell

## and brain diseases to discover therapies

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#### Supplementary Information

#### Supplementary Figures



**Figure S1. Overview of the enriched top 30 KEGG signaling pathways in the target tissues of the four diseases, related to Figure 1**. Gene set enrichment analysis (GSEA) of (A) T1D, (B) T2D, (C) MS, and (D) AD using the KEGG database. Bars in red and blue represent positive and negative enrichment in the associated pathways, respectively. The x-axis shows the normalized enrichment score (NES) of the *fGSEA* analysis, and the y-axis shows the enriched pathways with an adjusted *P*-value <0.05.

•		T1D upre	gulated ge	enes		T1D downregulated genes						
A	Motif	Name	P-value	% of Target % of Background Sequences with Sequences with Motif Motif		Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif		
	EASTITCASIA TGASIES	bZIP:IRF	1.00E-04	46.13%	35.42%	<b>AACCIICSATGGCTCCCIALIGCC</b>	C ZNF16	1.00E-03	6.15%	1.54%		
	SAAASE GAAASE	IRF2	1.00E-04	19.64%	11.97%	<b>êtgatgşaa</b> i	Atf4	1.00E-02	34.62%	22.59%		
	GRAASIGAAASI	IRF8	1.00E-03	44.35%	35.09%	ATTTCCALL	NFAT	1.00E-02	78.46%	66.29%		
	GAAASIGAAASI	IRF1	1.00E-03	23.21%	15.96%	SCATTGTATCCASA	Oct4:Sox17	1.00E-02	21.54%	12.36%		
	GGAAGTGAAASI	PU.1:IRF8	1.00E-03	30.36%	22.57%	GGAGCTGTCCAICGTGCTGA	REST-NRSF	1.00E-02	5.38%	1.41%		
	ACTITCGTTICI	T1ISRE	1.00E-02	3.57%	1.22%	<b>ESPATCAAT</b>	Cux2	1.00E-02	46.92%	34.69%		
	SASCTOSISSES AGATAA	GATA:SCL	1.00E-02	17.86%	12.08%	<b>EFTGIGGTIA</b>	RUNX-AML	1.00E-02	65.38%	54.57%		
	AITTICCALI	NFAT	1.00E-02	74.40%	66.73%							
	SCACCTCFESS	MyoD	1.00E-02	74.40%	67.06%							
	AAASAGGAAGIG	SpiB	1.00E-02	35.42%	28.15%							

B	izo upregulated genes										
5	Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif						
	SAAASIGAAASI	IRF2	1.00E-05	18.14%	11.81%						
	GAAASIGAAASI	IRF1	1.00E-05	22.71%	15.72%						
	SCAPSTGEES	Twist2	1.00E-05	94.79%	89.76%						
	ATTIGCATO ASAATS	-NANOG	1.00E-05	22.56%	15.90%						
	<b>CATCTGIE</b>	NeuroG2	1.00E-04	91.96%	86.44%						
	<b>ESCACCTGFESS</b>	MyoD	1.00E-04	75.08%	67.48%						
	<b>EESCAPETGE</b>	BHLHA15	1.00E-04	89.75%	84.10%						
	<b>ZAACAGCTG</b>	Tcf21	1.00E-04	80.60%	73.89%						
	GRAAEIGAAAEI	IRF8	1.00E-04	42.11%	34.65%						
	<b>SECAISTORE</b>	TCF4	1.00E-04	91.01%	85.91%						

T2D downregulated genes												
Motif	Name	P-value	% of Targets Sequences with Motif	% of Background Sequences with Motif								
GEECTGTCCATCGTGCTGA	REST-NRSF	1.00E-05	4.22%	1.23%								
<u> </u>	Sp5	1.00E-03	89.36%	83.91%								
200000222222	Sp2	1.00E-03	94.58%	90.41%								
<b>ESERATCAAT</b>	Cux2	1.00E-03	46.39%	39.03%								
<u>SGTCCCCCCCCC</u> SS	KLF14	1.00E-03	95.78%	91.98%								
<u>IGGGGA</u> AGG <u>S</u> E	ZNF467	1.00E-03	82.13%	76.00%								
<b>SEIGETGASASE</b>	Tbx20	1.00E-02	26.31%	20.49%								
GŞCEGTTE	MYB	1.00E-02	95.38%	92.04%								
ZIATEGAIEZ	HNF6	1.00E-02	52.81%	46.41%								
ÇÇATTÇTE	Sox3	1.00E-02	89.56%	85.32%								

C		MS	upregulate	ed genes	MS downregulated genes					
C	Motif	Motif Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif		Motif	Name	P-value	% of Targ Sequences Motif
	<b>ETTCC</b>	👌 STAT4	1.00E-03	81.06%	70.57%		<b>€€€CAGCTG</b>	Ap4	1.00E-06	87.16%
	ITCIAGAASETTC	Te HRE	1.00E-03	31.72%	21.63%		<b>ECITATCIES</b>	Gata6	1.00E-05	71.28%
	<b>FETGASTCAES</b>	Atf3	1.00E-03	56.39%	45.20%		<b>CACCTGETE</b>	Tcf12	1.00E-04	80.24%
	<u> AAFGIGIFAA</u>	Tbr1	1.00E-03	88.99%	80.57%			GATA3	1.00E-04	85.64%
	<b>ŁĘ<u>R</u>AGT</b> GĘĘ	Bapx1	1.00E-02	97.80%	93.01%		<b>AGATAASASS</b>	TRPS1	1.00E-04	92.23%
	<b>Zetgaetca</b> z	BATF	1.00E-02	54.63%	44.32%		SEEGACAATSS	Sox7	1.00E-03	33.61%
	CAACCZCASS	SF1	1.00E-02	50.22%	40.31%		<b>ATGEATAISE</b>	Pit1	1.00E-03	68.41%
	<b>ŽŽĘTĢAĘTÇA</b> Ę	Fra1	1.00E-02	49.78%	40.05%		<b>TABLE CAGE TGE</b>	Tcf21	1.00E-03	78.55%
	<b>ZZĘTĘAĘTÇA</b> Ł	Fos	1.00E-02	51.10%	41.55%		<b>ZATGS</b> AAIZE	Brn1	1.00E-03	32.94%
	<b>XOTGASTCA</b>	🛓 JunB	1.00E-02	48.90%	39.56%		ÉFÉCASCTGE	E2A	1.00E-03	91.05%

Motif	Name	P-value	Sequences with Motif	% of Background Sequences with Motif
<b>SECAGCTG</b>	Ap4	1.00E-06	87.16%	78.78%
<b>ECITATCIES</b>	Gata6	1.00E-05	71.28%	62.43%
<b>ECAGCTGETE</b>	Tcf12	1.00E-04	80.24%	73.03%
	GATA3	1.00E-04	85.64%	79.49%
<b>AGATAASES</b> S	TRPS1	1.00E-04	92.23%	87.28%
<b>SESEGACAATSG</b>	Sox7	1.00E-03	33.61%	26.58%
ATGRATAIS	Pit1	1.00E-03	68.41%	61.05%
<b>AGECAGCTGE</b>	Tcf21	1.00E-03	78.55%	71.96%
<b>ATGEPAATEE</b>	Brn1	1.00E-03	32.94%	26.23%
<b>SASCAGCTGE</b>	E2A	1.00E-03	91.05%	86.27%

П	AD upregulated genes											
D	Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif							
	<b>SERECTOICIALACASE</b>	Fox:Ebox	1.00E-03	80.26%	68.11%							
	AITTICCAII	NFAT	1.00E-02	82.89%	72.51%							
	<b>SEFITCCEE</b>	Fli1	1.00E-02	90.79%	82.29%							
	GAGECCGAGC	ZNF519	1.00E-02	38.16%	27.93%							
	<b>CCEATAAA</b>	Hoxd13	1.00E-02	93.42%	86.42%							
	<del>qaq</del> gtaaa <b>c</b> a	FOXA1	1.00E-02	86.18%	78.03%							
	ITTTAI	HOXB13	1.00E-02	84.21%	75.85%							
	<b>SEREACAATGG</b>	Sox7	1.00E-02	37.50%	28.25%							
	<u>IGTTIALIIAC</u>	FoxD3	1.00E-02	76.32%	67.09%							
	<del>atgatgatecagge</del>	ZNF165	1.00E-02	26.97%	18.85%							

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% of Target % of Backgrour	
Motif Name P-value Sequences with Sequences wit Motif Motif	10 h
CCATCCTCCTCA REST- NRSF 1.00E-02 4.97% 1.59%	
Motif CATCOTECTCA REST- NRSF 1.00E-02 4.97%	Motif 1.59%

Figure S2. Transcription factor binding site motif analysis reveals potential upstream regulators of the modified genes in the four diseases, related to Figure 1. The promoter regions (transcription start site ± 2kb) of the differentially expressed genes in each disease were analyzed using HOMER tools to predict known transcription factor binding site motifs. Tables show the sequence motifs, name, P-value and frequency (%) in target as well in background sequences. Top 10 transcription factor binding sites enriched in up- and downregulated genes of (A) T1D, (B) T2D, (C) MS and (D) AD are displayed



Figure S3: Venn diagrams of differentially expressed genes in T1D, T2D, MS and AD in bulk RNA-seq data, related to Figure 1. Venn diagrams of (A) upregulated and (B) downregulated genes in the four diseases. Differential expression was assessed with  $DESeq2 \ 1.28.1$  and genes were selected with an adjusted *P*-value <0.10 (Benjamini Hochberg correction). Sample sizes for the data are as follows: T1D (n = 4 for patients, n = 10 for controls); T2D (n = 28 for patients, n = 183 for controls); MS (n = 5 for patients, n = 5 for controls; AD (n = 122 for patients, n = 80 for controls).



**Figure S4. Functional enrichment analysis of overlapped genes among the four diseases, related to Figures 2 and 3.** Genes significantly overlapped between different pairs of diseases detected in the RRHO analysis (Figure 2) were selected for enrichment analysis using the *clusterProfiler* via the KEGG database. The top 20 gene sets are represented according to their adjusted P-values (Benjamini Hochberg correction) and their gene ratio (no. of modified genes/gene set size). Enriched pathways by genes significantly (A) upregulated both in T2D and T1D, (B) downregulated both in T2D and T1D, (C) upregulated both in T2D and AD, (D) downregulated both in T2D and AD, (E) upregulated both in T2D and MS, (F) upregulated both in MS and T1D, (G) upregulated both in AD and T1D are displayed.

Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif
GCTGASTCAGC	A MafK	1.00E-04	30.00%	19.71%
<b>ACCTCISAA</b>	Tbx6	1.00E-02	85.00%	77.13%
SATGASTCAJES	Fosl2	1.00E-02	35.77%	26.98%
ATTICCATAACAAI	OCT4-SOX2-	1.00E-02	21.54%	14.62%
	Twist2	1.00E-02	95.38%	90.34%
GATCACTCACCA	MafA	1.00E-02	68.46%	60.23%
	NF-E2	1.00E-02	8.08%	4.28%
TLAULETRE	HIF2a	1.00E-02	48.08%	40.11%
GGAAATICCC	NFkB-p65-Rel	1.00E-02	12.69%	7.96%
<b>EYGGYATIYC</b>	NFkB-p65	1.00E-02	65.77%	58.06%

	Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif
	IFFCTCCCCA	ZNF416	1.00E-04	93.33%	83.44%
	<b>FERSCAPETORE</b>	Atoh1	1.00E-03	84.62%	74.07%
ççêç	CTGICCAIGGTGCTG/	REST-	1 00E-03	5 13%	1 33%
	SECTOCS	NRSF	1.002-00	0.1070	1.0076
\$	AGAACAZARTGTIC	Znf263	1.00E-03	98.46%	93.00%
_	ACCATOTOLI	PGR	1.00E-02	29.74%	20.69%
	TCAACCTCA	Olig2	1.00E-02	96.41%	90.68%
		Nr5a2	1.00E-02	66.67%	56.39%
1		ZNF675	1.00E-02	24.10%	16.14%
		Pax7	1.00E-02	16.92%	10.24%
	AZUIGIZAZE	Tbet	1.00E-02	81.03%	72.45%

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C	Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif	Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif
	<u> <u><u></u></u><u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u><u></u></u></u>	Tlx	1.00E-03	50.38%	39.27%	GGAGCTGTCCATGGTGCTGA	REST-NRSF	1.00E-10	8.79%	1.40%
	ATTOPOCAAC	CEBP	1.00E-03	63.26%	52.85%	<b>CATSTGIE</b>	Olig2	1.00E-03	96.65%	90.84%
	<b>CAGCTGSES</b>	Tcf12	1.00E-03	79.92%	70.88%	TAACCCITISATE	ZNF652	1.00E-03	36.40%	26.32%
	AAASAGGAABTG	SpiB	1.00E-03	37.88%	28.65%	GAGSCCGAGC	ZNF519	1.00E-03	46.03%	35.47%
	SICAIGIGAC	MITF	1.00E-02	71.21%	62.76%	ATGSATAATICA	Pit1	1.00E-02	37.24%	28.18%
	<b>FETCIAGAAFETTCTAG</b>	HRE	1.00E-02	24.24%	17.23%	<b>AGGGGATTICCS</b>	NFkB-p65	1.00E-02	65.69%	56.29%
	<b>ITEECGEGAAAA</b>	E2F	1.00E-02	14.02%	8.65%	<b>ZZIAASSIAATÇA</b> SE	DUX4	1.00E-02	8.79%	4.36%
	ATTTCCTGE EW	S:ERG-fusi	on 1.00E-02	71.97%	63.64%	<b>EAATCASIGC</b>	Gfi1b	1.00E-02	59.83%	50.40%
	<b>ESCAGCTGEES</b>	MyoD	1.00E-02	71.59%	63.63%	<b>FREESESSOCICA</b>	EAR2	1.00E-02	89.12%	82.39%
	ITCIAGAASETTCIE	HRE	1.00E-02	30.30%	23.16%	CCCCTCCCCAC	Zfp281	1.00E-02	47.28%	38.83%

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Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif		Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif
IICIAGAASEIICIA	HRE	1.00E-03	31.42%	22.17%		GRAAEIGAAAEI	IRF8	1.00E-03	47.35%	35.58%
AGLILC AGLILC	ISRE	1.00E-02	12.64%	7.32%		AAASAGGAAGTG	SpiB	1.00E-03	38.78%	28.39%
STACTICICICCCA	Zfp809	1.00E-02	48.28%	39.18%		AGTTICASTTIC	IRF3	1.00E-03	44.49%	33.83%
<b>ETTCC:CGAA</b> E	STAT4	1.00E-02	79.31%	71.20%		<b>AGGGRATTICCS</b>	NFkB-p65	1.00E-03	66.53%	56.35%
FETCIACAAFETTCLAGA	HRE	1.00E-02	24.90%	17.93%		SEC CARTESARS	Hoxd10	1.00E-02	80.41%	71.62%
GAAABIGAAABI	IRF1	1.00E-02	22.22%	15.69%		ISTGACCARIAG	Bcl11a	1.00E-02	69.39%	60.54%
<u> <u> <u> </u></u></u>	VDR	1.00E-02	33.33%	26.20%		GAAASIGAAASI	IRF1	1.00E-02	23.27%	16.27%
IGCTGACISA	MafA	1.00E-02	67.82%	60.15%		<u><u><u><u></u></u></u></u>	Tlx	1.00E-02	50.61%	41.88%
SECATATIAC	Six1	1.00E-02	29.89%	23.19%		<b>ASCACGTG</b>	NPAS	1.00E-02	89.39%	83.16%
						<b>GLC+CCICLESECS</b>	ZNF317	1.00E-02	14.69%	9.38%
	Motif ITCIAGAAS&TTCIA ASTTTCASTTTC SAMECIAGUEGGAA &ITTCCASGAAA &ITTCCASGAAA SELICIXGAASTTCLASA GAAASIGAAASI SAAGTCASIAGUICASS STETCASISTIAC	Motif Name   IIICIAGAASETICIA HRE   ASTIICASTICIA HRE   SSTECIASICIONA Zfp809   ELETICOSCIONA STATA   SELEXICASETICIASE HRE   GAAASIGAASE IRF1   SSACIGASCIONALSI IRF1   SSACIGASCIONALSI IRF1   SSACIGASCIONALSI Name   SACICASTACICASES VDR   ICCIGACISA MafA   SSETCASZETICI Six1	Motif     Name     P-value       IICLACAASTICLA     HRE     1.00E-03       ASTICASTIC     ISRE     1.00E-02       STRECTOURGEA     Zfp809     1.00E-02       STRECTOURGEA     STAT4     1.00E-02       STATE     INOE-02     STAT4       MAASTICASSTICLASS     IRF1     1.00E-02       SAAASTICASSTICASST VDR     INCE-02       STATASTICASTA     MafA     1.00E-02       STATASTICASTA     MafA     1.00E-02       STATASTICASTA     Six1     1.00E-02	Motif     Name     P-value     % of Target Sequences with Motif       IICLACAASTICLA     HRE     1.00E-03     31.42%       ASTICASTICLA     HRE     1.00E-02     12.64%       STRECIZECIONA     Zfp809     1.00E-02     12.64%       STRECIZECIONA     Zfp809     1.00E-02     48.28%       STLEXCAASTICLASSE     HRE     1.00E-02     79.31%       STLEXCAASTICLASSE     HRE     1.00E-02     24.90%       GAAASTICLASSE     HRE     1.00E-02     22.22%       SAGGTCASTACTICASSE     VDR     1.00E-02     33.33%       ICCTCASTA     MafA     1.00E-02     67.82%       STETCASTACTICASSE     Six1     1.00E-02     29.89%	Motif     Name     P-value     % of Target Sequences with Motif     % of Background Sequences with Motif       IIICLACATETICLE     HRE     1.00E-03     31.42%     22.17%       ACTITCACTICLE     HRE     1.00E-02     12.64%     7.32%       STRUCTACTICLE     HRE     1.00E-02     12.64%     7.32%       STRUCTACTICLE     HRE     1.00E-02     48.28%     39.18%       CLICLESCARE     STAT4     1.00E-02     79.31%     71.20%       STATA     1.00E-02     24.90%     17.93%       GAAASTICLACATION     HRE     1.00E-02     22.22%     15.69%       STATA     1.00E-02     33.33%     26.20%       ICCTGACTSA     MafA     1.00E-02     29.89%     23.19%	Motif     Name     P-value     % of Target Sequences with Motif     % of Background Sequences with Motif     % of Background Sequences with Motif     F       IIICIAGA%TICIA APTICASTIC     HRE     1.00E-03     31.42%     22.17%       APTICASTIC     ISRE     1.00E-02     12.64%     7.32%       APTICASTIC     ISRE     1.00E-02     48.28%     39.18%       ATTICASTANA     STAT4     1.00E-02     79.31%     71.20%       APTICASTGAASTICIAGE     HRE     1.00E-02     24.90%     17.93%       QAAASTICAAAST     IRF1     1.00E-02     23.33%     26.20%       ICCTCASTSA     MatA     1.00E-02     29.89%     23.19%	Motif     Name     P-value     % of Target Sequences with Motif     % of Background Sequences with Motif     F       IIICLAGASSITICE     HRE     1.00E-03     31.42%     22.17%     Motif     9000000000000000000000000000000000000	Motif     Name     P-value     % of Target Sequences with Motif     % of Background Sequences with Motif     F       IIICIAGASSTICIA ADTICATION SETUCATION STREETICA	Motif     Name     P-value     % of Target Sequences with Motif     % of Background Sequences with Motif     F       IIICLAGATETICA AETITCATICA SECONDECTICATION SECONDECTION SECONDECTICATION SECONDECTICATION SECONDECTICATION SEC	Motif     Name     P-value     % of Target Sequences with Motif     % of Background Sequences with Motif     F       IIICIAGAM%ITCL4     HRE     1.00E-03     31.42%     22.17%     Motif     Name     P-value     % of Target Sequences with Motif       IIICIAGAM%ITCL4     HRE     1.00E-03     31.42%     22.17%      AAASIGAAASI     IRF8     1.00E-03     47.35%       Motif     USE     1.00E-02     12.64%     7.32%      AAASIGAAASI     IRF8     1.00E-03     38.78%       Motif     USE-02     48.28%     39.18%      SPIB     1.00E-03     38.78%       Motif     USE-02     79.31%     71.20%     SECOMANTICLS     NFB-p65     1.00E-02     80.41%       GAAASIGGAAASI     IRF1     1.00E-02     22.22%     15.69%     SECOMASICAASES     Bd11a     1.00E-02     80.41%       IICTGACESA     MarA     1.00E-02     33.33%     26.20%     IITGACASES     Bd11a     1.00E-02     23.27%       IICTGACESA     MarA     1.00E-02     29.89%     23.19

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G .	Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif	п	Motif	Name	P-value	% of Target Sequences with Motif	% of Background Sequences with Motif
	AAASAGGAASIG	SpiB	1.00E-04	41.49%	28.87%		AAAGAGGAAGTG	SpiB	1.00E-06	43.02%	28.66%
	<b>ESCAPGTGEE</b>	NPAS2	1.00E-03	80.08%	70.46%		<b>ETTCC:</b> GGAA	STAT4	1.00E-03	83.40%	73.63%
	AGAGGAAGTG	PU.1	1.00E-03	61.00%	50.47%		AGAGGAAGTG	PU.1	1.00E-03	60.75%	50.44%
	<u>GRAASIGAAASI</u>	IRF8	1.00E-02	46.47%	36.97%		SAGITICAGIATGASISS	bZIP:IRF	1.00E-03	49.43%	39.59%
	ACTITCGTTICI	T1ISRE	1.00E-02	4.15%	1.42%	9	<b>ACATCERSEACATCERSE</b>	p53	1.00E-02	12.83%	7.58%
	TICIAGAASSIICIA	HRE	1.00E-02	31.54%	23.64%		£\$\$\$CAIGISS\$\$\$CAIGFS	p63	1.00E-02	38.11%	29.70%
	<b>EGECAGTTEE</b>	AMYB	1.00E-02	91.70%	85.72%		<b><u>SCCCCCCC</u></b>	NEkB-p50	1.00E-02	26 79%	19 38%
	<b>Zecacgtg</b>	NPAS	1.00E-02	88.80%	82.58%		<b><u><b>STCCC</b>ASESTCCC</u>A</b>	Tiv	1.00E-02	47 92%	39.60%
	<b>SICAIGIGAC</b>	MITE	1.00E-02	71.37%	63.31%		ACTITCGTTICI	TISPE	1.00E-02	3 77%	1 30%
	GGAASTGAAASI F	PU.1:IRF8	1.00E-02	31.12%	23.75%		GAAASIGAAASI	IRF1	1.00E-02	23.77%	17.37%

**Figure S5. Transcription factor binding site motif analysis reveals the potential TFs controlling commonly up- or downregulated genes in pairs of diseases, related to Figures 2 and 3**. The promoter regions (transcription start site ± 2kb) of the top 300 commonly up- or downregulated genes in each pair of diseases from RRHO analysis (Figure 2) were analyzed using the *HOMER* tools. Tables show the sequence motifs, name, *P*-value and frequency (%) in target as well as in background sequences. Top 10 transcription factor binding sites enriched in genes (A) upregulated in T2D and T1D, (B) downregulated in T2D and T1D, (C) upregulated in T2D and AD, (D) downregulated in T2D and AD, (E) upregulated in T2D and MS, (F) upregulated in MS and T1D, (G) upregulated in MS and AD, (H) upregulated in AD and T1D.



Figure S6. Bromodomain inhibitors attenuate cytokine-induced pro-inflammatory gene expression in EndoC- $\beta$ H1 cells, related to Figures 4 and 5. EndoC- $\beta$ H1 cells were pretreated for 6 h with the bromodomain inhibitors iBET-151 (1  $\mu$ M, grey bars) or GSK046 (1  $\mu$ M, black bars) and then exposed to IFN $\gamma$  (1000 U/ml) and IL1 $\beta$  (50 U/ml) or not (non-treated, NT) for 24 h. mRNA expression of *HLA-ABC*, *CXCL10*, *IL-8* and the ER stress markers *CHOP* and *BiP* were analyzed by quantitative real-time PCR. Values were normalized to the geometric mean of the reference genes  $\beta$ -actin and VAPA; the highest value of each experiment was considered as 1. (F) The percentage of apoptotic cells was counted after 24 h by Hoechst 33342 and propidium iodide staining. Results are mean  $\pm$  SEM of 5-7 independent experiments. \*p<0.05, \*\*p<0.005, \*\*\*p<0.001 and \*\*\*\*p<0.0001 by ANOVA followed by Bonferroni correction for multiple comparisons.



Figure S7. Bromodomain inhibitors attenuate cytokine-induced pro-inflammatory gene expression in EndoCβH1 cells, related to Figures 4 and 5. EndoC- $\beta$ H1 cells were pretreated for 6 h with the bromodomain inhibitors iBET-151 (1 µM, grey bars) or GSK046 (1 µM, black bars) and then exposed to IFNγ (1000 U/mI) and IL1 $\beta$  (50 U/mI) or not (non-treated, NT) for 48 h. mRNA expression of *HLA-ABC*, *CXCL10*, *IL-8* and the ER stress markers *CHOP* and *BIP* were analyzed by quantitative real-time PCR. Values were normalized to the geometric mean of the reference genes  $\beta$ -actin and VAPA; the highest value of each experiment was considered as 1. (F) The percentage of apoptotic cells was counted after 48 h by Hoechst 33342 and propidium iodide staining. Results are mean ± SEM of 5-7 independent experiments. \*p<0.05, \*\*p<0.005, \*\*\*p<0.001 and \*\*\*\*p<0.0001 by ANOVA followed by Bonferroni correction for multiple comparisons.

Supplementary Tables

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-	Disease	Target tissue	Mean TPM in	Mean TPM in	TPM ratio	log <sub>2</sub> fold	Adjusted P-
			controls	cases		change	value
	T1D	Pancreatic β-cells	2.6 ± 2.0	15.7 ± 18.1	5.9	1.8	0.069
	T2D	Pancreatic islets	1.0 ± 0.6	1.8 ± 1.2	1.7	0.59	0.006
	MS	Optic chiasm	9.3 ± 4.2	21.7 ± 20.3	2.3	0.74	0.587
	AD	Prefrontal cortex	6.3 ± 3.0	8.1 ± 5.2	1.3	0.36	0.023

#### Table S1. Expression of leukocyte marker CD45 in the target tissues of four diseases, related to Figure 1.

CD45 gene expression is displayed as mean ± standard deviation of TPM (Transcript per Million) in cases and controls of the four diseases. Gene expression was quantified using *Salmon 1.4.0*. Mean TPM and TPM ratio were calculated for cases and controls. The log<sub>2</sub> fold change (considering both fold change and estimation for dispersions) and adjusted *P*-value (Benjamini-Hochberg correction) were computed by R package *DESeq2 1.28.1*.

	Age (years)	Gender	BMI (kg/m <sup>2</sup> )	Cause of death	β-cell purity (%)
Donor 1	63	Male	21.2	CVD	37
Donor 2	78	Male	25.5	CVD	63
Donor 3	78	Female	26.7	CVD	59
Donor 4	86	Female	22.9	CVD	63
Donor 5	91	Female	22.2	CVD	65
Donor 6	89	Female	23.4	CVD	20
Donor 7	49	Female	31.2	CVD	53
Donor 8	78	Female	25.7	CVD	54

Table S4. Characteristics of human islet donors, related to Figures 5, 6, and 7.

BMI (body mass index); CVD (cardiovascular disease).  $\beta$ -cell purity was assessed by immunostaining for insulin.

Gene	Primer sequence (5' -> 3')	Direction	
ACTR	CTGTACGCCAACACAGTGCT	Forward	
ACTB	GCTCAGGAGGAGCAATGATC	Reverse	
	TACCGAAACAAGGAAACTAATGGAA	Forward	
VAFA	GCCTTAAACCTTCATCTCTCAGGT	Reverse	
	GTGGCATTCAAGGAGTACCTC	Forward	
CACETO	GCCTTCGATTCTGGATTCAG	Reverse	
	CAGGAGACACGGAATGTGAA	Forward	
TILA-ABC	TTATCTGGATGGTGTGAGAACC	Reverse	
11.6	AAAAGATGGCTGAAAAAGATGG	Forward	
12-0	CTACTCTCAAATCTGTTCTGG	Reverse	
11 .0	TGTAAACATGACTTCCAAGCT	Forward	
12-0	TTGGAGTATGTCTTTATGCAC	Reverse	
	AGAACATCCAAAGTGTGAAC	Forward	
UXUL I	TTTCTTAACTATGGGGGATG	Reverse	
colicod VPD1	CCGCAGCAGGTGCAGG	Forward	
	GAGTCAATACCGCCAGAATCCA	Reverse	
RID	Oiagen QuantiTect primer, cat# OT00006404	Forward	
DIF		Reverse	
CHOR		Forward	
UNUF	Qiagen QuantiTect primer, cat# QT00082278	Reverse	

Table S5. Sequence of quantitative real-time qPCR primers, related to Figures 5, 7, S6 and S7.