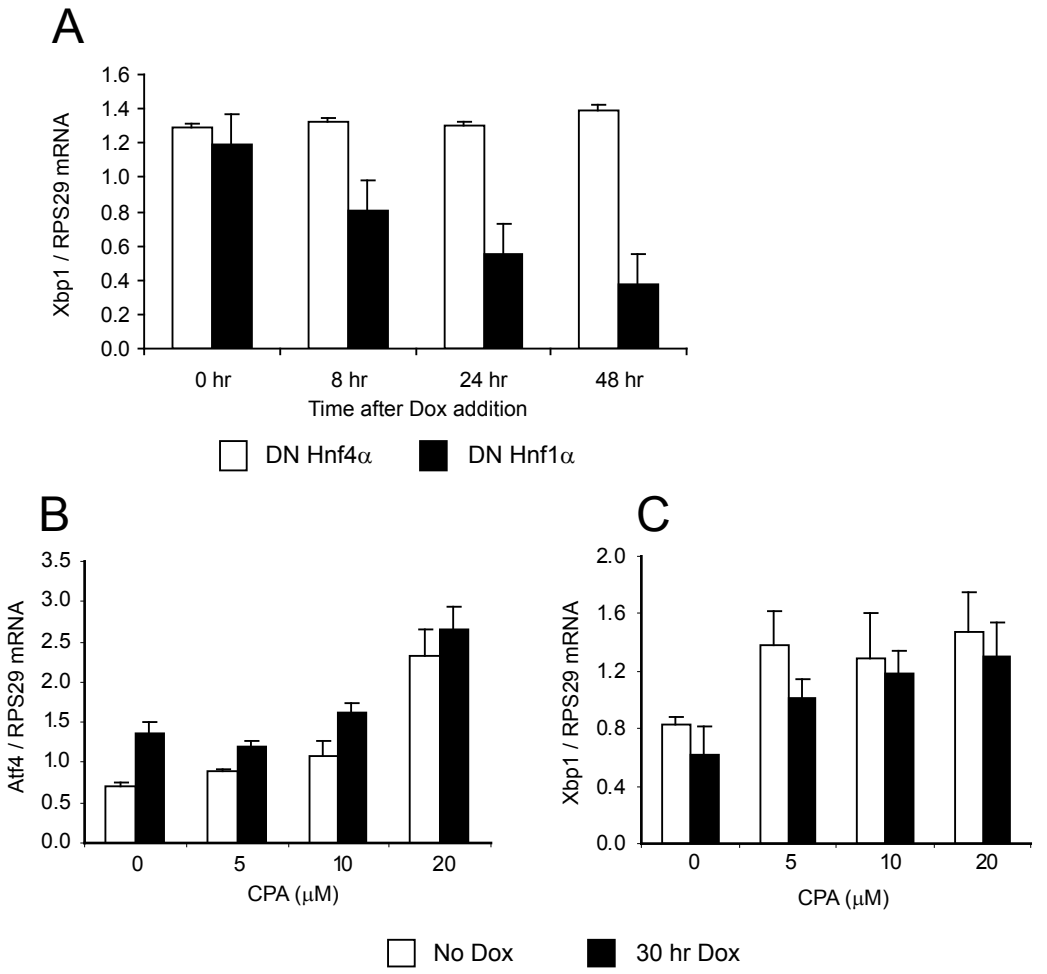
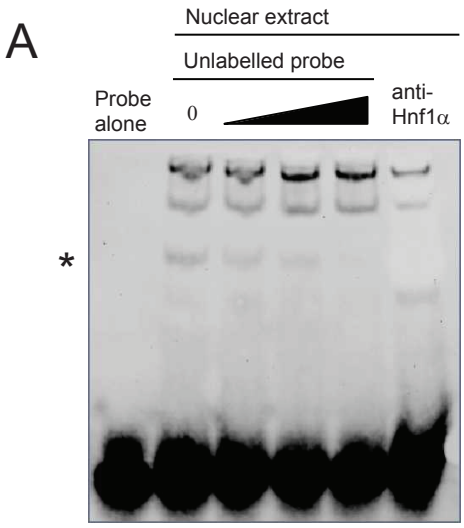
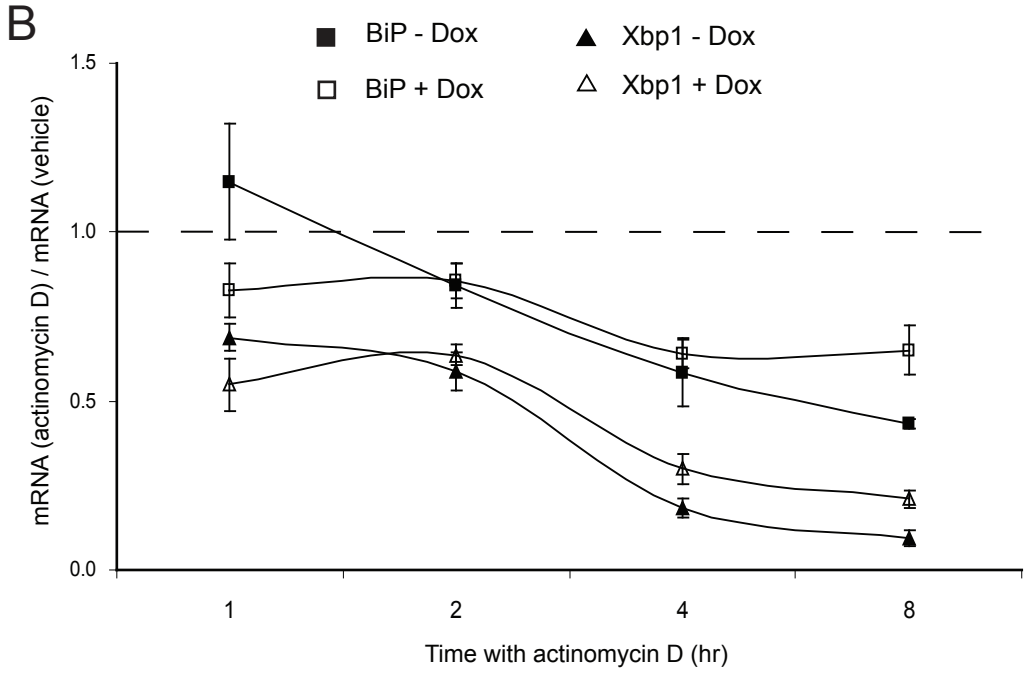


Supplemental Figure 1. (A) Timecourse of Xbp1 mRNA levels after Dox in DN Hnf4α and DN Hnf1α expressing cells. Transcription of Atf4 (B) and Xbp1 (C) in response to CPA is not affected by DN Hnf1α induction.





Supplemental Figure 2. (A) Competition EMSA to demonstrate specific binding of Hnf1α to the Xbp1 promoter. The band corresponding to unique binding of Hnf1α to the probe is marked with an asterisk. The unlabelled probe was used at 100x, 200x and 400x the concentration of the biotin-labelled probe. The nuclear extract was prepared from INS DN Hnf1α cells without Dox. (B) Time course of BiP and Xbp1 mRNA degradation after ActD. INS DN Hnf1α cells were cultured +/- Dox for 24 hr, vehicle (DMSO) or ActD (5 μg/ml) was added and RNA collected at the indicated time points. Data are expressed as the ratio of mRNA in the ActD-treated sample to mRNA in the vehicle-treated control, mean ± SEM of three to four independent experiments. The dotted line indicates a value of 1, corresponding to zero degradation of the RNA.

A

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aatgtgaaga
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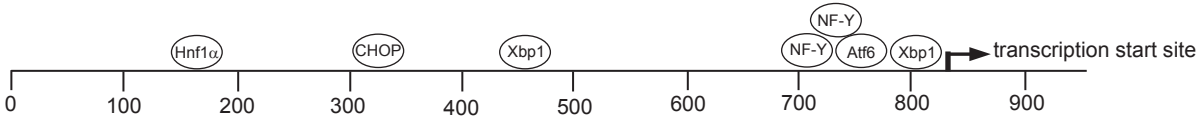
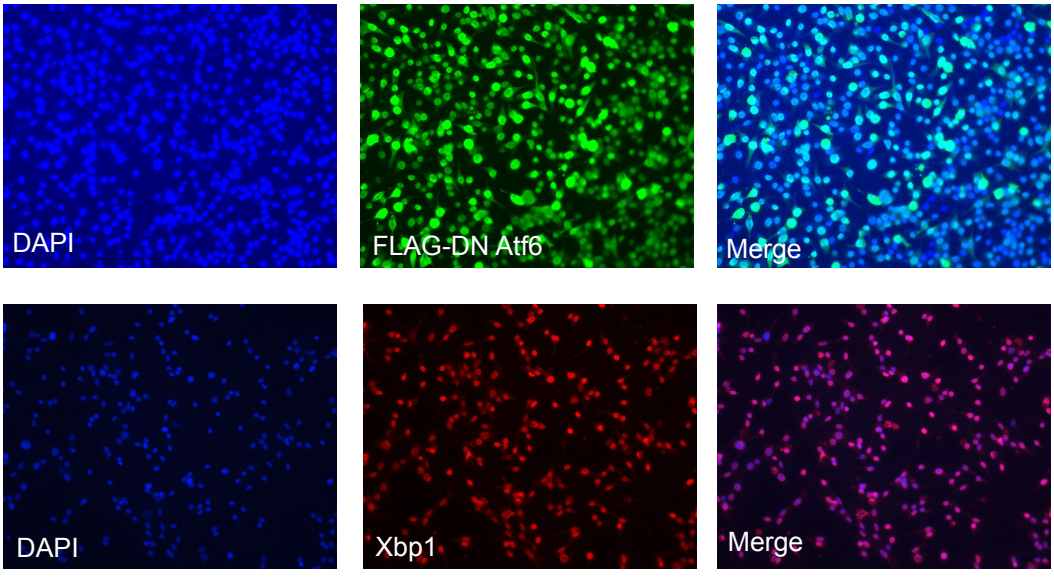
B

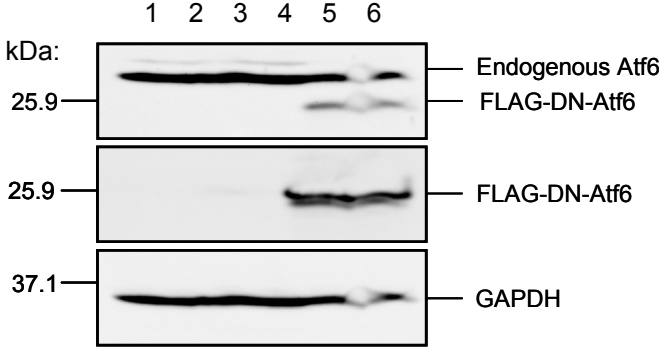


Supplemental Figure 3. (A) Sequence of the cloned Xbp1 promoter with putative transcription factor binding sites coloured as follows: red, Hnf1α; blue, CHOP; orange, Xbp1; green, NF-Y; magenta, Atf6. The transcription start site is underlined. (B) Graphical representation of the cloned promoter indicating the positions of putative transcription factor binding sites. Sites were detected by comparison against the TransFac database with the program Match set to minimise false negatives.

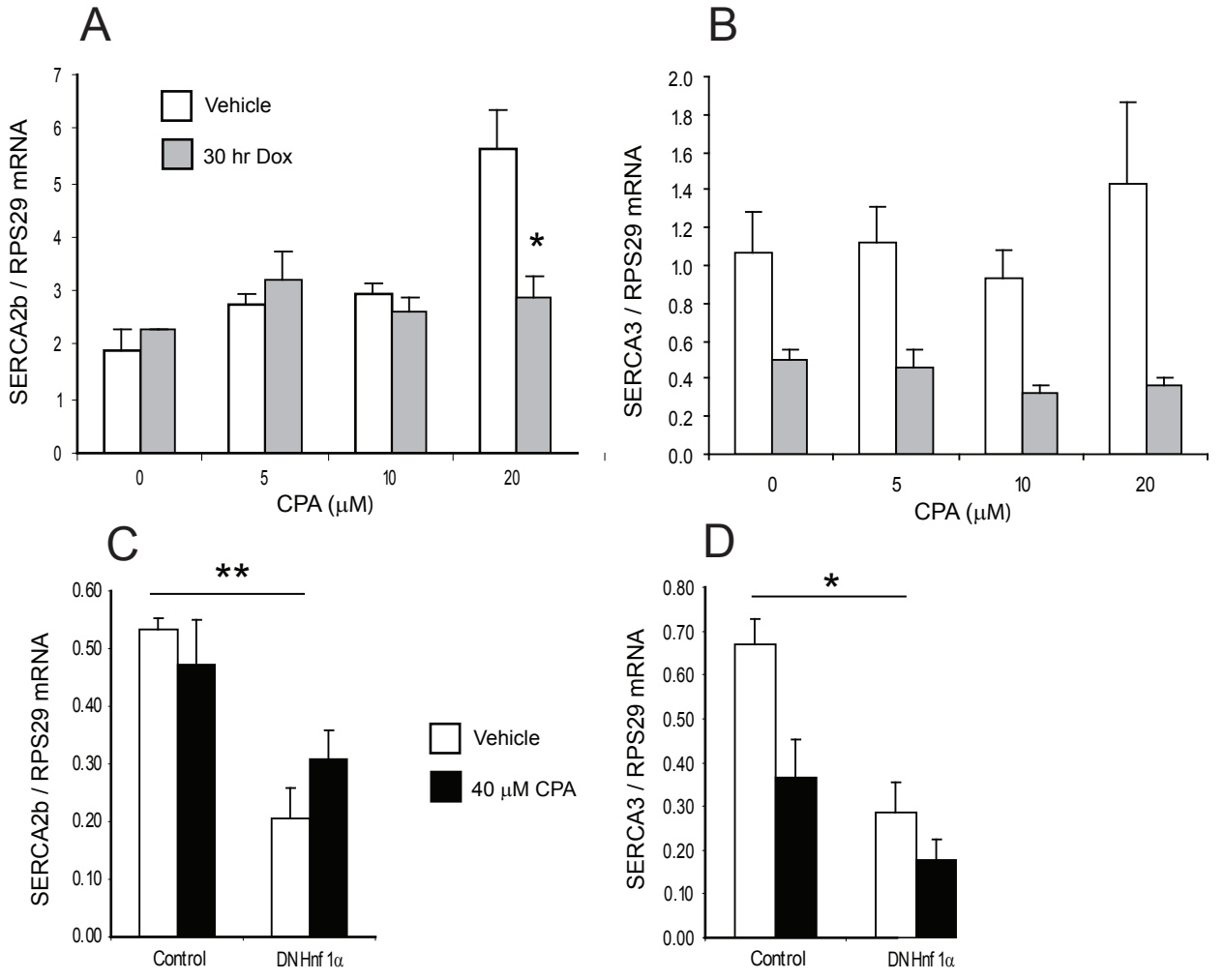
A



B



Supplemental Figure 4. (A) 20 adenovirus units per cell of Ad-DN Atf6 and Ad-DN Xbp1 is sufficient to achieve infection rates approaching 100 %. When immunofluorescence was performed under these conditions in the absence of adenovirus, no fluorescence was visible for either of the antibodies. Images are at 20 x magnification. (B) Control Western blotting of extracts from INS-1E cells (lanes 1 and 2), INS-1E + Ad-LacZ adenovirus (lanes 3 and 4) and INS-1E + Ad-DN-Atf6 adenovirus (lanes 5 and 6). Extracts for each condition were prepared from separate cell cultures. The anti-Atf6 antibody was from Santa Cruz (#sc-22799) since the antibody used in Figure 4 did not recognise the DN-Atf6 from the adenovirus. Top panel, anti-Atf6; middle panel, anti-FLAG (Sigma Aldrich); bottom panel, anti-GAPDH (Millipore).



Supplemental Figure 5. SERCA gene expression in DN Hnf1α cells (A and B) and mice (C and D). Expression of SERCA2b (ubiquitous) and SERCA3 (restricted to β-cells within the islet) was measured in DN Hnf1α cells pre-exposed to Dox for 24 hours followed by CPA or vehicle for 6 hours, and in mouse islets cultured overnight followed by CPA or vehicle for 6 hours. Data are displayed as mean ± SEM, n = 3 for all experiments.
* indicates $p < 0.05$, ** indicates $p < 0.01$.

Supplemental Table S1. Sources and dilution factors of primary antibodies for Western blotting.

Protein	Source	Catalogue number	Dilution
Hnf1α	A gift from Dr R. Cortesi (University of Pomezia, Italy)	None	1/4000
BiP	Cell Signaling Technology (Bioconcept, Allschwil, Switzerland)	CST #3183	1/800
Xbp1	Santa Cruz Biotechnology (Santa Cruz, CA 95060, USA)	sc-7160 (M-186)	1/100
Atf6	Lifespan Biosciences (Seattle, WA 98121, USA)	LS-C3480	1/400
GAPDH	Sigma (Basel, Switzerland)	G9545	1/20000

Supplemental Table S2. Oligonucleotide sequences used in this work for Q-PCR.

Primer name	Sequence (5' – 3')
rATF4_5'	TGGCCATCTCCCAGAAAGTG
rATF4_3'	GGGAAGAGGCTGCAAGAATG
rBIP_5'	CACGTCCAACCCGGAGAAC
rBIP_3'	TTCCAAGTGCGTCCGATGA
rCHOP_5'	GGAAAGTGGCACAGCTTGCT
rCHOP_3'	CTGGTCAGGCGCTCGATT
rDNAJC3_5'	TGAAGCTGCCCAGGAACAG
rDNAJC3_3'	AGTAACCGCTGGGCTTTCTCT
rPDI_5'	AGACAAGGACGTGCTGATCGA
rPDI_3'	GTACTTGGGTTCCAGGTTCTTACAG
rXBP1_5'	TTGTCACCTCCCCAGAACATC
rXBP1_3'	AAAGGATATCAGACTCAGAATCTGAAGA
rXBP1_NDN_5'[a]	CTCAGTGAAGAAAGAACCTTTGGAT
rXBP1_NDN_3'[a]	GCTGGATGAAAGCAGGTTTGA
rATF6_NDN_5'[b]	GCCATGGAGTCGCCTTTTAG
rATF6_NDN_3'[b]	AAACAACGTGGACTCCCAGTCT
rRPS29_5'	GCTGAACATGTGCCGACAGT
rRPS29_3'	GGTCGCTTAGTCCAACTTAATGAAG
mBIP_5'	ACCCCGAGAACACGGTCTT
mBIP_3'	GCTGCACCGAAGGGTCATT
mCHOP_5'	CCACCACACCTGAAAGCAGAA
mCHOP_3'	AGGTGAAAGGCAGGGACTCA
mXBP1_5'	ATCAGCTTTTACGGGAGAAAACTC
mXBP1_3'	CCATTCCCAAGCGTGTTCTT
mRPS29_5'	CACGGTCTGATCCGCAAAT
mRPS29_3'	GCGTACTGCCGGAAGCA
mCYCLO_5'	CATGATCGGGAGGGTTTGC
mCYCLO_3'	TGATAAAGAACTGAGAGCCATTCG

a) Used to detect endogenous Xbp1 in the presence of the DN Xbp1 adenovirus
b) Used to detect endogenous Atf6 in the presence of the DN Atf6 adenovirus

Supplemental Table S3. Oligonucleotide sequences used in this work for ChIP, EMSA and Xbp1 promoter cloning.

Primer name	Sequence (5' – 3')
chip_ins1_5'	CTCTGGGACAATGATTGTGCTG
chip_ins1_3'	GTCGTAATTTCCAAACACTTGCC
chip_xbp1_5'	AAATGTATTCTCCCTGTGCAAACTT
chip_xbp1_3'	GGTCTAGGCCAGCTGAAGCA
rMyoD1_S	AGGAGTAGGCACTGGAGAGACTT
rMyoD1_AS	GCCTCAAGCCAATAGGAGTGTAG
xbp1_biot_20_5'[a]	AGTTATTAATTAATTAATCA-biotin
xbp1_biot_20_3'[b]	TGATTAATTAATTAATAACT-biotin
xbp1_5'[c]	GTCAGGCTCCAGCGCAGCAA
xbp1_3'[c]	CCCGGAACCATGAGCGGCAG

a) Sense strand of the EMSA probe for Hnf1α binding to the Xbp1 promoter
b) Antisense strand of the EMSA probe for Hnf1α binding to the Xbp1 promoter
c) PCR primers for cloning the Xbp1 promoter segment containing the Hnf1α binding site