Developmental Cell *14*

Supplemental Data

Synergistic Function of E2F7 and E2F8 Is Essential for Cell Survival and Embryonic Development

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Supplemental Experimental Procedures

Electromobility Shift Assay (EMSA) for DNA Binding

EMSAs were performed as described before (Maiti et al., 2005). Briefly, E2F7 proteins were translated *in vitro* using the TNT Quick coupled transcription/translation system (Promega) following the manufacturer's protocol. The fragment of the adenoviral E2 promoter containing two E2F-binding sites was used as a probe for binding under conditions previously described. LightShift chemiluminescent EMSA kit (Pierce) was employed for visualization and detection.

Cell Proliferation Assay

To measure the proliferation of cre-treated *wild type* and *E2f7*$^{loxP/loxP}$*E2f8*$^{loxP/loxP}$ primary cells, 2x10^5 MEF cells were seeded in 60mm dishes and counted daily in triplicate for 7 days using a Beckton Dickson Coulter Counter.

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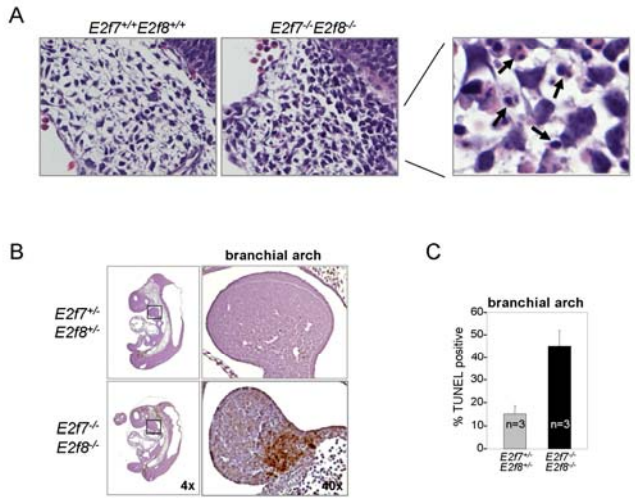

Figure S1. Inactivation of *E2f7* and *E2f8* Induces Massive Apoptosis in E9.5 Embryos

(**A**) H&E staining of E9.5 embryo mesenchymal tissues. The right panel highlights the nuclear morphology of mesenchymal cells in *E2f7*$^{-/-}$*E2f8*$^{-/-}$ embryos; black arrows point to examples of pyknotic nuclei. (**B)** Formalin fixed sections of embryos with the indicated genotypes were analyzed by TUNEL assays. Far left panels: low magnification pictures of whole embryos. Right panel: high magnification images of representative areas demarcated by the box in the low magnification images. (**C**) Quantification of TUNEL-positive cells in the branchial arch areas is presented as the average ± SD percentage of cells that are TUNEL-positive. Three sections per embryo and three different embryos for each genotype were analyzed.

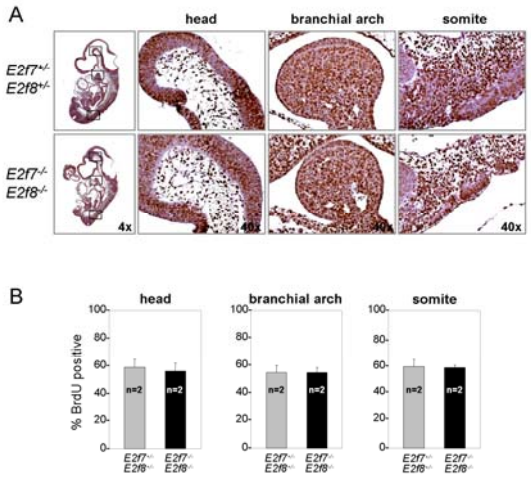

Figure S2. Inactivation of *E2f7* and *E2f8* Does Not Affect BrdU Incorporation In Vivo

(**A**) BrdU staining of embryos with the indicated genotypes. Far left panels: low magnification pictures of whole embryos. Right three panels: high magnification images of representative areas demarcated by the box in the low magnification images. (**B)** Quantification of proliferation in different tissue areas of embryos is presented as the average ± SD percentage of cells that are BrdU-positive. Three sections per embryo and two different embryos were counted for each genotype group.

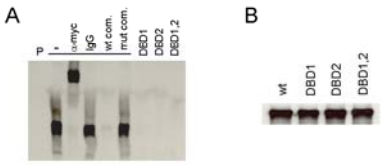

Figure S3. DNA Binding Mutations Abolish the DNA Binding Activity of E2F7

(**A**) EMSAs of *in vitro* translated myc-tagged *wild type* or mutant forms of E2F7 containing amino acid substitutions (Maiti et al., 2005) in the indicated DNA binding domains (DBD1, DBD2, DBD1,2) using a biotin-labeled E2 DNA probe. *In vitro* translated reactions of *wild type* E2F7 were incubated with mock buffer (-), anti-myc or IgG antibodies as indicated, or incubated with an unlabeled *wild type* (wt com.) or mutant E2 (mut com.) probe. (**B**) Western blot of *in vitro* translated *wild type* or mutant forms of myc-tagged E2F7 using anti-myc antibodies.

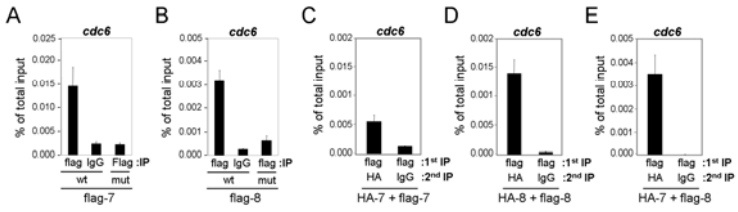

Figure S4. E2F7 and E2F8 Bind to the *cdc6* Promoter

(**A-E**) The same chromatin-immunoprecipitated DNA that was used and described in Figure 4F-J was amplified using primers specific for the *cdc6* promoter. Real-time PCR was performed in triplicate and cycle numbers were normalized to 1% of the input DNA.

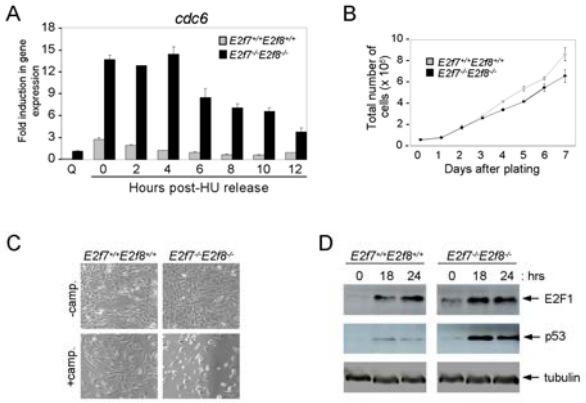

Figure S5. MEFs Deficient in *E2f7* and *E2f8* Are Hypersensitive to DNA Damage Induced Apoptosis

(**A**) Total RNA isolated from same synchronized MEFs samples as in Figure 4F was analyzed by real-time RT-PCR assays specific for *cdc6* expression. (**B**) Growth curve of cre-treated $E2f7^{+/+}E2f8^{+/+}$ and $E2f7^{loxP/loxP}E2f8^{loxP/loxP}$ MEFs. Cells were plated and viable cells counted daily in triplicate. For convenience, cre-deleted *loxP* alleles were labeled as (-/-). (**C**) Light microscopy images of MEFs treated as in Figure 4G at 72h. (**D**) Lysates derived from MEFs treated as in Figure 4G were analyzed by Western blotting using E2F1 and p53 specific antibodies. Tubulin-specific antibodies were used as an internal loading control.

Gene	Fold induction (log2)	Function	Reference
		Stress Related	
Stc2	3.91	hypoxia, nutrient response, calcium and phosphate homeostasis	Ito et al., 2004
Ier3	3.26	hypoxia response, apoptosis	Chen et al., 2006
Pdk1	2.96	hypoxia response, carbohydrate metabolism	Kim et al., 2007
Bhlhb2	2.92	hypoxia, genotoxic, DNA damage response, apoptosis	Olbryt et al., 2006
Trib3	2.83	hypoxia, nutrient response, insulin signaling and glucose homeostasis, apoptosis	Wu et al., 2007
Ddit4	2.74	hypoxia, DNA damage response, apoptosis	Schwarzer et al., 2005
Ndrg1	2.64	hypoxia response, cell differentiation	Jin et al., 2002; Kasper et al., 2005
Adm	2.64	hypoxia response, angiogenesis	Olbryt et al., 2006
Vldlr	2.42	hypoxia response, lipid metabolism	Kasper et al., 2005
Ndrg1 /// Ndrl	2.37	hypoxia response, cell differentiation	Jin et al., 2002; Kasper et al., 2005
Ndrl	2.37	hypoxia response, cell differentiation	Jin et al., 2002; Kasper et al., 2005
Pfkp	2.26	hypoxia response, glycolysis	Olbryt et al., 2006; Kasper et al., 2005
Aldoc	2.25	hypoxia response, glycolysis	Olbryt et al., 2006
Bnip3	2.20	hypoxia response, apoptosis	Olbryt et al., 2006; Kasper and Brindle, 2006; Martin-Rendon et al., 2007
Pkp2	2.17	hypoxia response, adhesion	Olbryt et al., 2006
Maff	2.16	hypoxia response, transcription	Chen et al., 2006; Kasper et al., 2005
Stc1	2.15	nutrient, hypoxia response, calcium homeostasis	Ito et al., 2004; Kasper and Brindle, 2006
Eno2	2.10	hypoxia response, glycolysis	Olbryt et al., 2006; Martin-Rendon et al., 2007
Pfkfb3	2.04	hypoxia response, glycolysis	Chesney et al., 20006
Slc16a3	2.03	hypoxia response, monocarboxylic acid transport	Ord et al., 2005
Nppb	2.00	hypoxia response, cardiovascular homeostasis	Olbryt et al., 2006
Egln3	1.98	hypoxia response, apoptosis	Kasper and Brindle, 2006; Kasper et al., 2005
Slc2a3	1.95	hypoxia response, glucose transport	Ragel et al., 2007; Zhang et al., 1999
Pgm2	1.92	hypoxia response, glycolysis	Manjunath et al., 1998
2310056P07Rik	1.91	hypoxia response	Kasper et al., 2005
Rora	1.90	including hypoxia response, cGMP metabolism, transcription	Zhu et al., 2006
Krt19	1.89	hypoxia response, cytoskeleton organization and biogenesis	Kasper et al., 2005
Ero1l	1.86	hypoxia response, oxidoreductase activity	Jin et al., 2002; Kasper et al., 2005
Ankrd1	1.85	hypoxia response, transcription corepressor activity	Samaras et al., 2006
Mt1	1.84	stress response, metal ion homeostasis	Emerson et al., 2000
Sesn2	1.79	hypoxia, DNA damage response, p53-dependent apoptosis	Budanov et al., 2004; Budanov et al., 2002
Rad51l1	1.74	DNA damage response, DNA repair	Thacker, 1999
Mt2	1.71	stress response, metal ion homeostasis	Emerson et al., 2000
Flt1	1.65	hypoxia response, angiogenesis	Kearney et al., 2004; Ahmed et al., 2000
Slc2a1	1.64	hypoxia response, glucose transport	Kasper and Brindle, 2006; Zhang et al., 1999
P4ha1	1.63	hypoxia response,, protein metabolism	Kasper et al., 2005
Pfkl	1.61	hypoxia response, glycolysis	Kasper and Brindle, 2006; Kasper et al., 2005

Gene	Fold induction (log2)	Function	Reference
		Stress Related (cont.)	
Hk2	1.60	hypoxia response, glycolysis	Olbryt et al., 2006, Kim et al., 2007
P4ha2	1.58	hypoxia response, protein metabolism	Kasper et al., 2005
Tmem45a	1.56	hypoxia response	Martin-Rendon et al., 2007
Ddit3	1.52	hypoxia, DNA damage response, p53-dependent apoptosis, transcription	Ragel et al., 2007; Jin et al., 2002; Liu et al., 2007
Tnfaip3	1.52	apoptosis	Beyaert et al., 2000
Vegfa	1.51	hypoxia response, angiogenesis	Olbryt et al., 2006; Ord et al., 2005; Kim et al., 2007; Martin-Rendon et al., 2007
		Others	
Klk1b22 /// Klk1b9	3.37	proteolysis	Chan et al., 1999
Ppp1r3c	2.59	glycogen metabolism	Printen et al., 1997
BC064011	2.28	NADH dehydrogenase, electron transport	
Rgs11	2.17	regulation of G-protein signaling	Giudice et al., 2001
Uck2	1.97	pyrimidine metabolism	van Rompay et al., 2001
Aox4	1.97	electron transport, oxidoreductase activity	
Scmh1	1.94	transcription corepressor activity	Tomotsune et al., 1999
Dtprp	1.90	decidual/trophoblast prolactin-related protein	Alam et al., 2006
Plekha2	1.80	phospholipid binding	Dowler et al., 2000
A2m /// LOC677369	1.73	protease inhibitor activity	van Leuven et al., 1992
Dbp	1.72	transcription, circadian rhythm	Gachon et al., 2006
Smyd3	1.71	chromatin modification, proliferation	Hamamoto et al., 2004
Ndrg2	1.68	nervous system development, differentiation	Nichols, 2003
Punc	1.66	neuronal cell adhesion	Yang et al., 2001
Tcfl5	1.59	transcription	Siep et al., 2004
St3gal1	1.58	protein amino acid glycosylation	
Pvr	1.57	adhesion, migration	Ikeda et al., 2003
Cbln3	1.57	transneuronal signaling	Bao et al., 2006
Loxl2	1.54	oxidoreductase activity	Csiszar, 2001
Pck2	1.53	gluconeogenesis	Beale et al., 2007
Upp1	1.52	nucleotide catabolism, uridine metabolism	Cao et al., 2005
Asah3l	1.50	lipid metabolism, ceramide metabolism	
		Unknown	
---	3.11	unknown	
2610528A11Rik	3.04	unknown	
Ankrd37	2.58	unknown	
A330076H08Rik	2.30	unknown	
4930583H14Rik	2.13	unknown	
2900016B01Rik	2.12	unknown	
2700089E24Rik	2.11	unknown	

Gene	Fold induction (log2)	Function	Reference
		Unknown (cont.)	
BC062258	2.10	unknown	
2210418O10Rik	2.04	unknown	
Gm129	2.02	unknown	
Zc3h6	1.98	unknown	
---	1.93	unknown	
Ppp1r3g	1.89	unknown	
4933409K07Rik /// LOC545605 /// LOC665845	1.87	unknown	
---	1.73	unknown	
---	1.70	unknow	
5830408C22Rik	1.68	unknown	
C330008K14Rik	1.61	unknown	
---	1.57	unknown	
---	1.57	unknown	
LOC676974	1.56	unknown	
B230112C05Rik	1.55	unknown	
---	1.53	unknown	

Figure S6. Functional Annotation of Gene Expression

Genes are indicated with their gene symbols, medium Log2-differentials between *wild type* and *E2f7*$^{-/-}$*E2f8*$^{-/-}$ samples, and gene functions (www.ncbi.nim.nih.gov/entrez). Based on their function annotations, 88 up-regulated genes are grouped in 3 categories and sorted in the descending order of Log2-differentails. References indicate previous reports for these genes function. For complete references list see Supplemental References.

Gene	Forward Primer	Reverse Primer
Genotyping		
E2f7	AGGCAGCACACTTGACACG	ACTTTTGGGACAGAGGTAGGA
		CCAAGATGAAGGCCGAGATGCTAC
E2f8	TAAAAAGCTTTGCGGTCGTT	AAGCCAACCTCGATGAATTG
		CTCGCATCATCGTCTGCTAA
Generating ISH Probes		
E2f7	TTGGCTTAGGCGGGTAGGAGACG	GGCTGGCGGCGCTGATGAG
E2f8	GTCGAATTCGGTACACCCTCTCCAAACCA	GACTCTAGAACCCGGAGTACGGAAGAAAT
Real-time RT-PCR		
E2f7	GCCAAGCAGGAAACAGAAGA	ACCGTGCCAACCATACTGAT
E2f8	GAGAAATCCCAGCCGAGTC	CATAAATCCGCCGACGTT
E2f1	GCCCTTGACTATCACTTTGGTCTC	CCTTCCCATTTTGGTCTGCTC
Cdc6	AGTTCTGTGCCCGCAAAGTG	AGCAGCAAAGAGCAAACCAGG
Gadd45	ACGACATCAACATCCTGCGG	CAAAGTCATCTCTGAGCCCTCG
Noxa	GATGAGGAGCCCAAGCCCAACC	CCCAAACGACTGCCCCCATACAA
Pidd	GCACCGTGTGAATCTCATTGC	CAGGAAGTGAACCCCGATAAAAG
Ndrg1	TCTTTGAGGCAGAGGGAGAA	CAATGAAATCACACCCACCA
Eco1L	CCGAAAAACTGATCGCAAAT	CAGAAACAGGCACATTCCAA
Pfkp	GGTTACTTGGCCTTGGTGAG	CGATTGCTCCTTCAGACACA
Slc2a3	AACTGTCCCCTCCTCCACTT	GCCCCTTTCCATAGCAATCT
Bnip3	GGGTTTTCCCCAAAGGAATA	GACCACCCAAGGTAATGGTG
Trib3	ACTTGGCTGTGGGATTCAAG	GACTGTGGGCCTGGGTACTA
Eomes	GTGACAGAGACGGTGTGGAGG	AGAGGAGGCCGTTGGTCTGTGG
Lect1	CACCAGCAGGAAGGAGAAAG	GGATTTACACCATGCCCAAG
Real-time ChIP-PCR		
E2f1-promoter	CTGCCTGCAAAGTCCCGGCCACTT	AGGAACCGCCGCCGTTGTTCCCGT
E2f1-exon1	CGCCCAGACGCCACTTCATC	TTCATTCCCTCACTCATTCAACAA
Tubulin-promoter	ATGGAGGGATGAATGGTTATGC	CTTTTTGGGTCTGGCTTCTTTCAC
Cdc6-promoter	AAAGGCTCTGTGACTACAGCCA	GATCCTTCTCACGTCTCTCACA

Figure S7. Primer Sequence Information for PCR Procedures