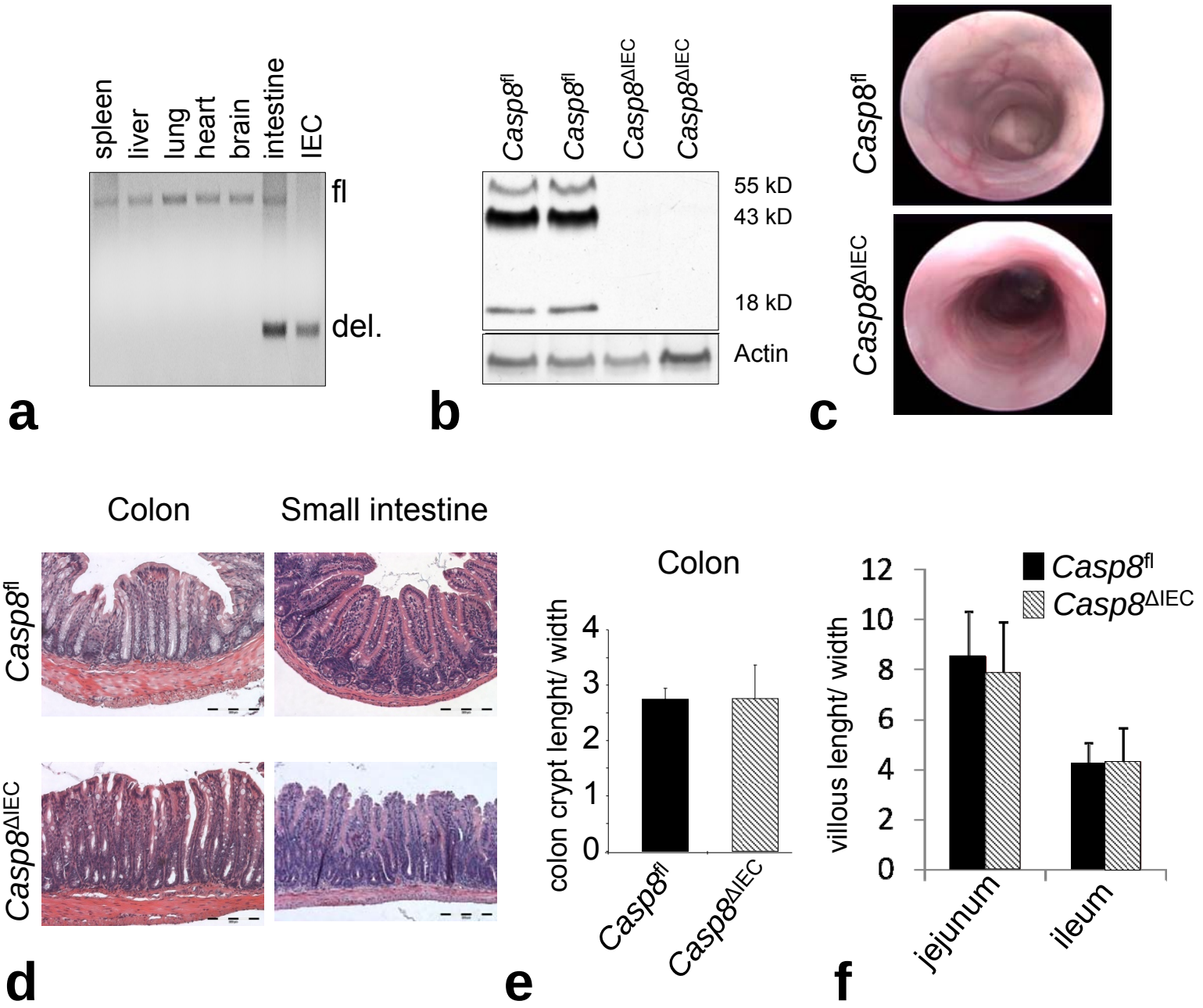
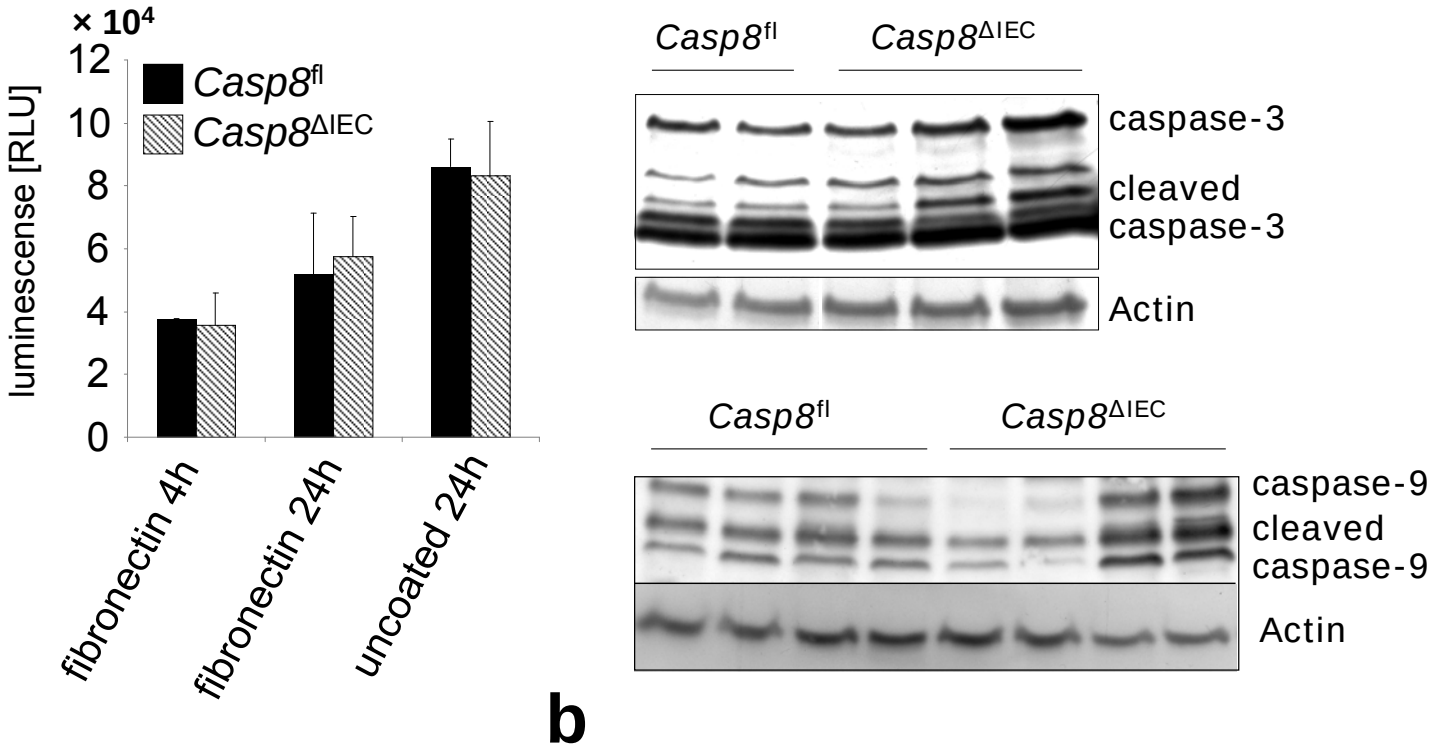
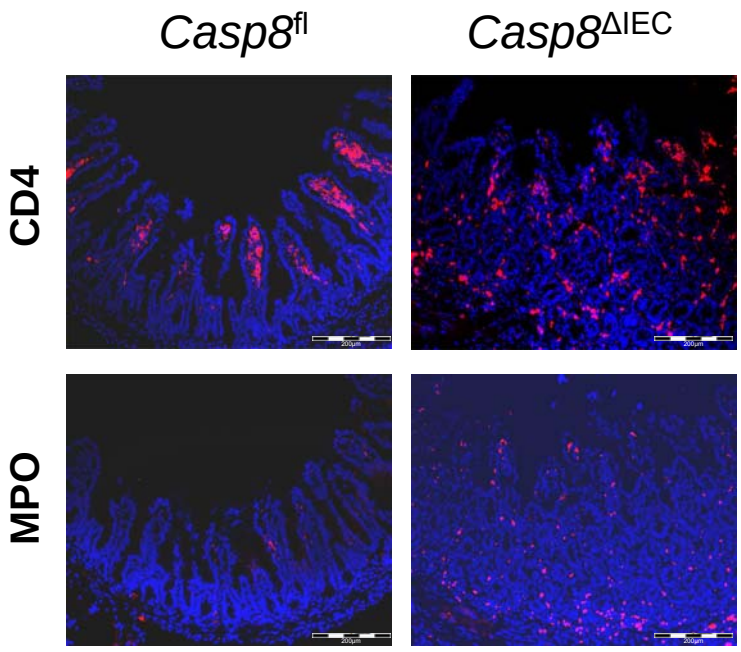


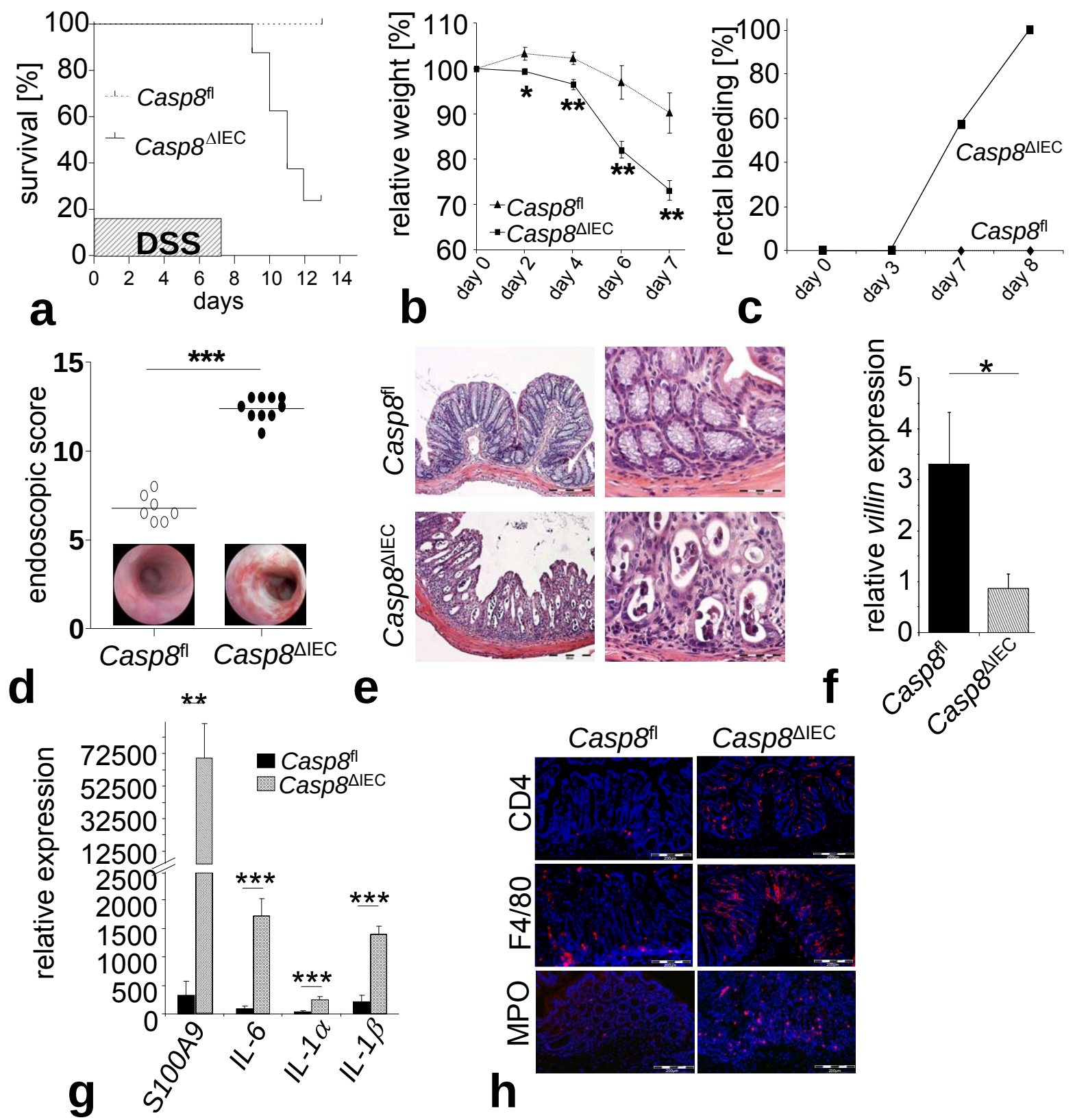
Suppl. Figure 1: Caspase-8 is not essential for the structural development of the gut.
(a) Generation of *Casp8*$^{\Delta IEC}$ mice. Presence of the Cre-deleted *caspase-8* allele (del.) selectively detected in gut IEC. DNA was isolated from different organs and subjected to an allele-specific PCR (fl = undeleted). **(b)** Western blot analysis for caspase-8 using IEC lysates from control and *Casp8*$^{\Delta IEC}$ mice. **(c)** Representative endoscopic pictures of the colon of control and *Casp8*$^{\Delta IEC}$ mice 6 weeks after birth showing normal morphology and the absence of inflammation. **(d)** H&E staining of paraffin-embedded colon and small intestine from 6 week old control and *Casp8*$^{\Delta IEC}$ mice. **(e+f)** Relative crypt and villous dimensions +SD calculated from H&E stained gut sections (n>=5 per group).



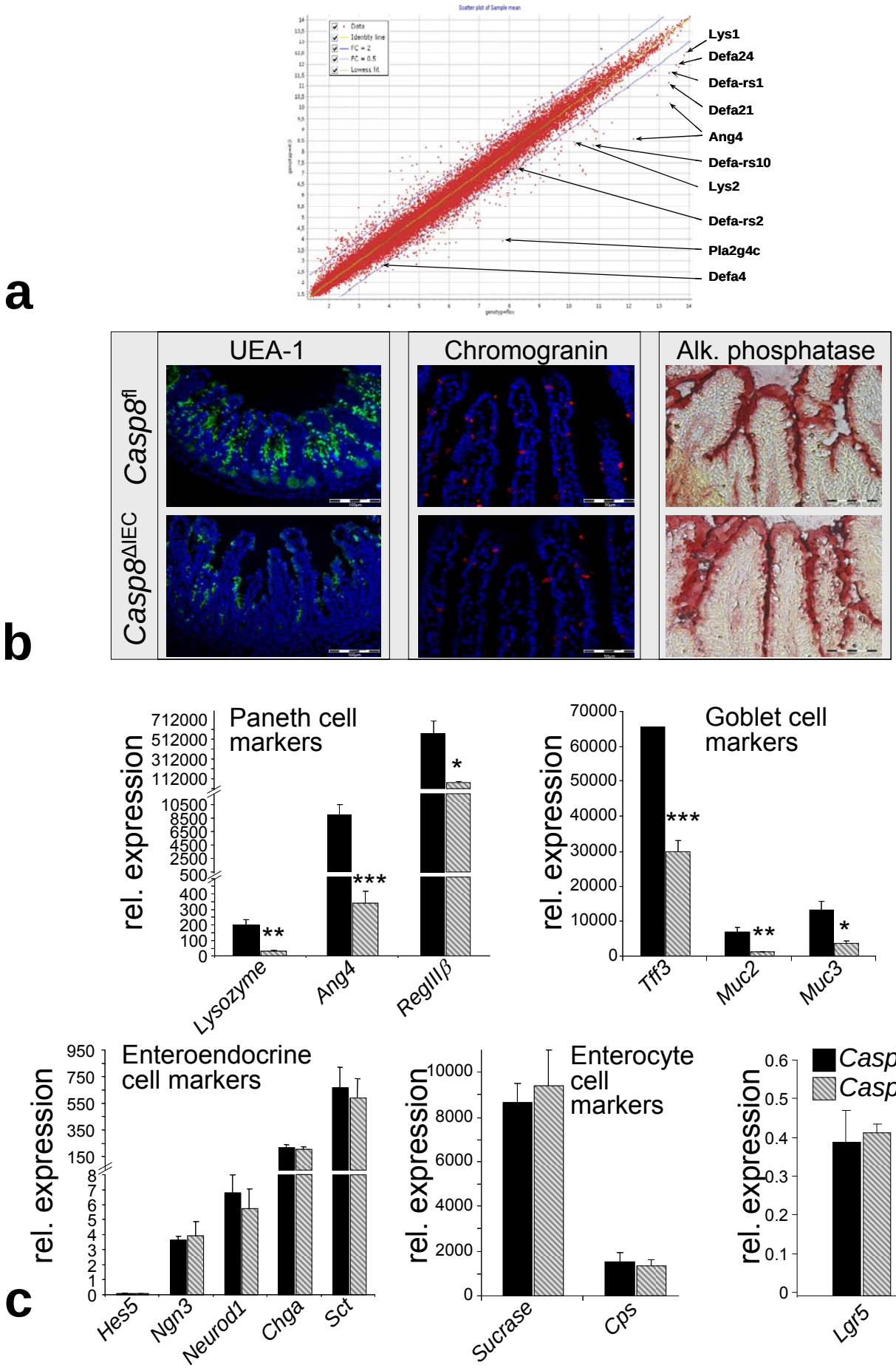
Suppl. Figure 2: Caspase-8 deletion did not result in apoptosis dysregulation of IECs.
(a) Quantification of caspase-3/-7 activity after 4 and 24 hours *in vitro* cultivation of isolated primary control and caspase-8 deficient intestinal epithelial cells (n = 2 mice per group, + SD) **(b)** Western blot for caspase-3 and caspase-9 expression and activation in IEC lysates from control and caspase-8 deficient mice. Beta-actin antibody was used as a loading control.



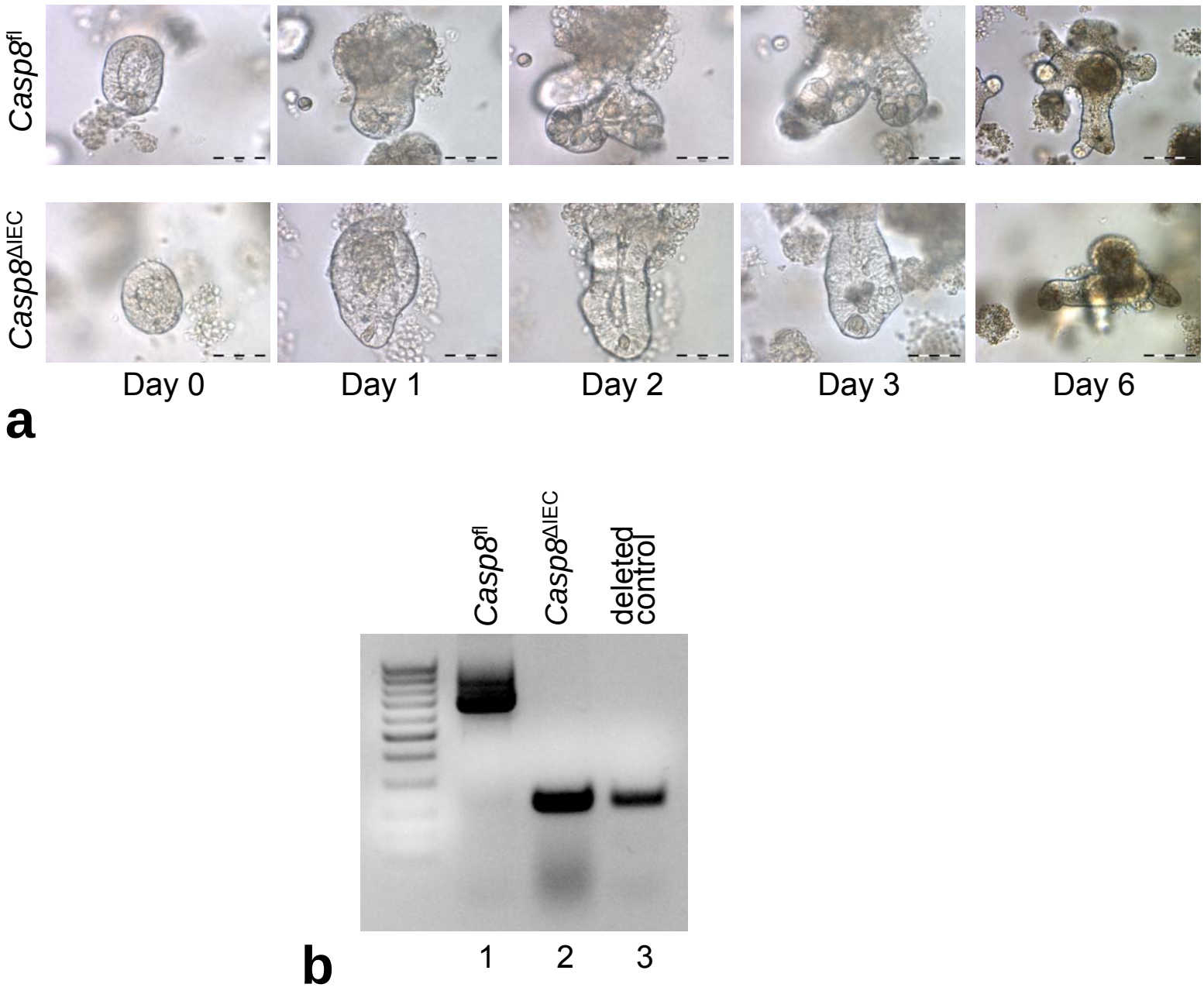
Suppl. Figure 3: Infiltration of the small intestinal lamina propria with immune cells.
Immunohistochemical detection of T cells (CD4) and granulocytes (MPO) in the terminal ileum of control and *Casp8*$^{\Delta IEC}$ mice.



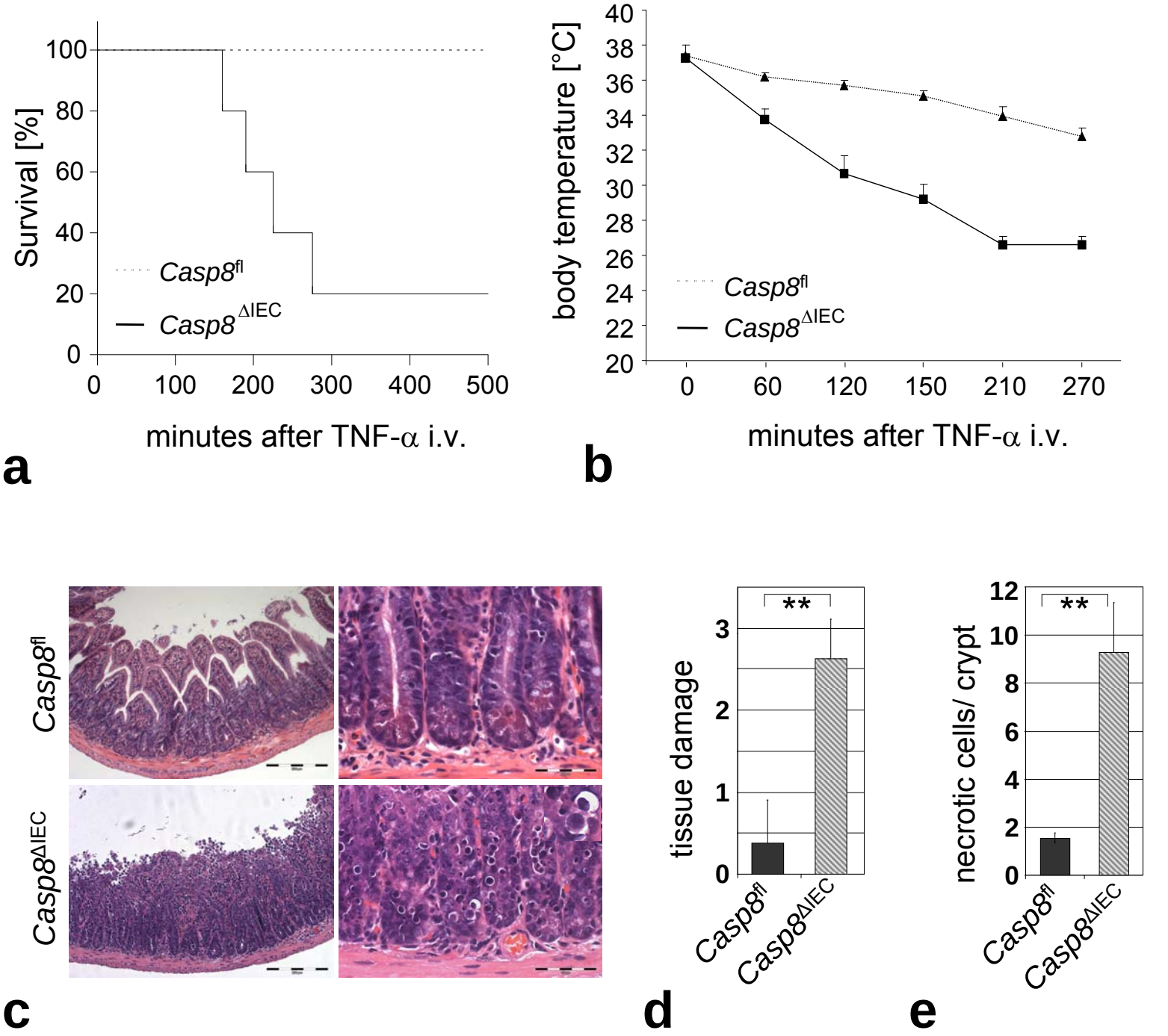
Suppl. Figure 4: *Casp8*$^{\Delta IEC}$ mice are highly susceptible to experimental colitis.
Control (n>6) and *Casp8*$^{\Delta IEC}$ (n>5) mice were treated with 1.5% (a) or 1% (b-h) DSS for 1 week. The experiment was repeated 5 times with similar results. **(a)** Kaplan-Meier survival curve **(b)** Weight loss was monitored over time and is indicated as % of the initial weight +/-SEM. **(c)** Percentage of mice showing rectal bleeding in response to DSS treatment. **(d)** Representative endoscopic pictures and endoscopic score of control and *Casp8*$^{\Delta IEC}$ mice after 7 days of DSS treatment. **(e)** Representative H&E stained colon cross sections of DSS treated control and *Casp8*$^{\Delta IEC}$ mice showing pronounced tissue damage with severe epithelial erosions. **(f)** Quantitative PCR for *Villin* expression in colon samples from control and *Casp8*$^{\Delta IEC}$ mice. Mean values relative to *HPRT* are shown +SEM (n>5). **(g)** Expression of pro-inflammatory cytokines and chemokines in colon tissue of control and *Casp8*$^{\Delta IEC}$ mice after DSS treatment (+SEM, relative to *HPRT*). **(h)** Colon cross sections from DSS treated control and *Casp8*$^{\Delta IEC}$ mice were immunostained with antibodies for myeloperoxidase (MPO), CD4 and F4/80. Representative pictures are shown.



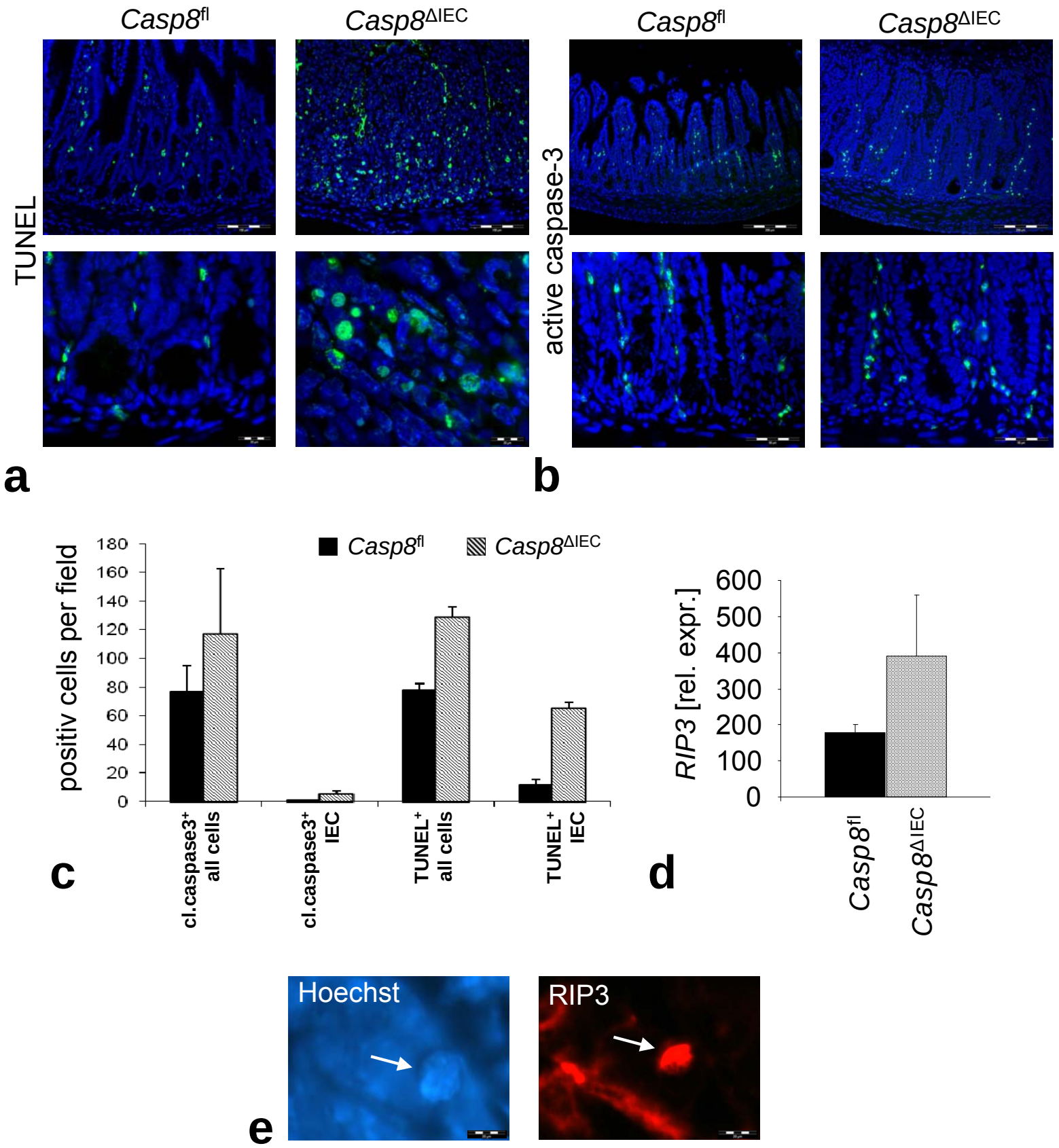
Suppl. Figure 5: Altered expression of antimicrobial genes in *Casp8*$^{\Delta IEC}$ mice.
(a) Prevalence of genes belonging to the family of antimicrobial peptides in the group of downregulated genes using gene chip (of IEC from 3 control and 3 *Casp8*$^{\Delta IEC}$ mice). The blue line indicates *p*-values < 0.05. **(b)** Cross sections from the ileum of 6 week old control and *Casp8*$^{\Delta IEC}$ mice were stained for different cell types using specific markers (UEA-1 for goblet cells, chromogranin-A for enteroendocrine cells and alkaline phosphatase for absorptive enterocytes). **(c)** Quantitative expression level of *Lgr5* and various terminal differentiation markers in isolated IEC from 5 week old control and *Casp8*$^{\Delta IEC}$ mice (n=10, mean values relative to HPRT +SEM).



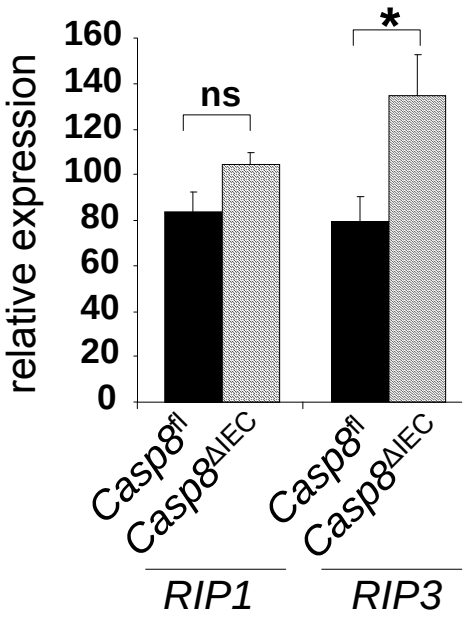
Suppl. Figure 6: Development of organoids from control and *Casp8*$^{\Delta IEC}$ mice.
(a) *In vitro* culture of crypts isolated from control and *Casp8*$^{\Delta IEC}$ mice as indicated in methods showing indistinguishable organoid development. **(b)** Allele-specific PCR confirmed the deletion of *caspase-8* in a Paneth cell positive organoid from a *Casp8*$^{\Delta IEC}$ mouse (lane 2).



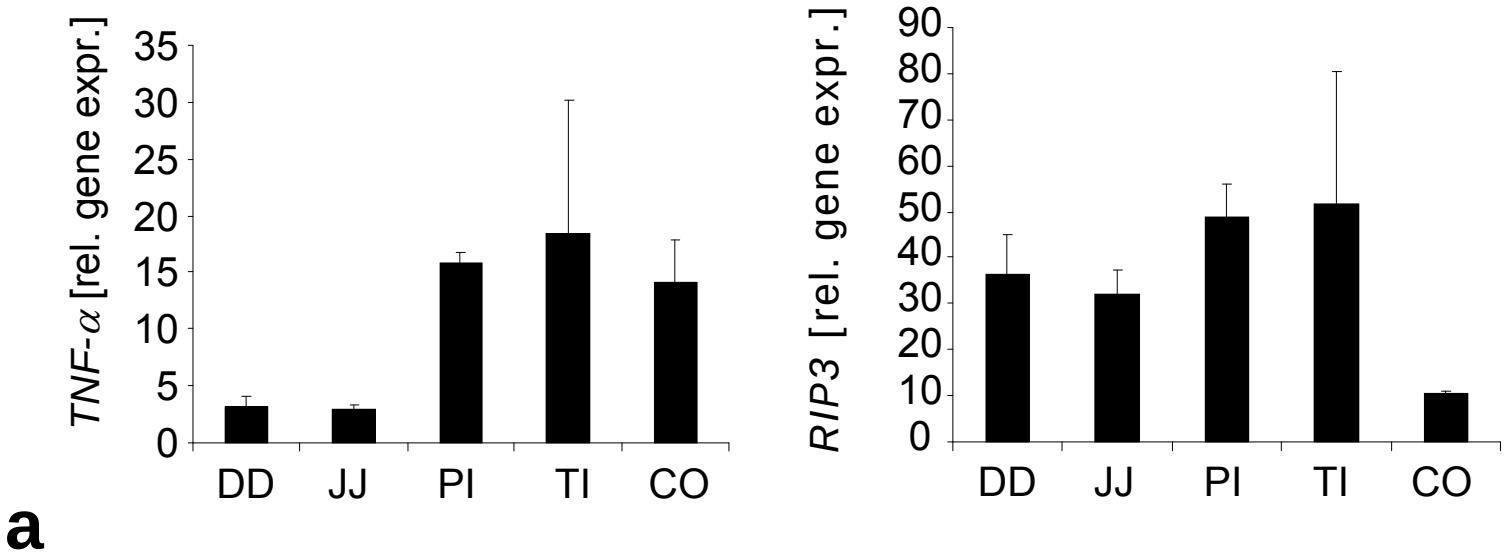
Suppl. Figure 7: Failure of *Casp8*$^{\Delta IEC}$ mice to control TNF-mediated pathology.
(a) Kaplan-Meier survival curve and **(b)** body temperature (+SD) of control (n=4) and *Casp8*$^{\Delta IEC}$ mice (n=5) after intravenous injection of TNF-α. **(c)** Representative histological pictures and **(c)** scoring (+SD) of tissue damage in the small intestine of TNF-treated mice 3 h after intravenous TNF-α injection. **(e)** Graph showing the number of necrotic cells (pyknotic nuclei and shrunken eosinophilic cytoplasm) per crypt (+SD) in cross sections from (c). Necrotic cells of each 10 crypts per animal were counted (n=6).



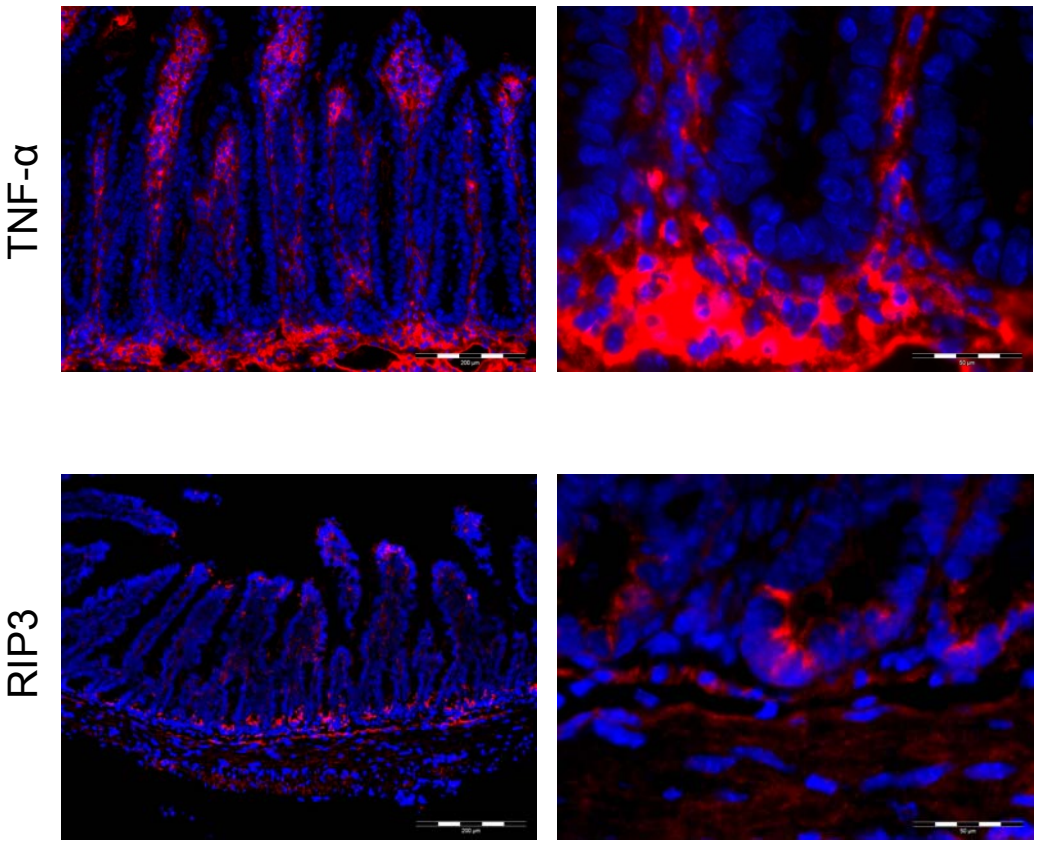
Suppl. Figure 8: Epithelial cell death after TNF-α injection.
Cross sections from the small intestine of TNF-treated control (n=3) and *Casp8*$^{\Delta IEC}$ (n=3) mice were stained for TUNEL **(a)** and active caspase-3 **(b)**. **(c)** Graph showing the average number of caspase-3 and TUNEL positive cells per microscopic field from (a) and (b) + SEM. **(d)** Quantitative RT-PCR analysis of *RIP3* in the terminal ileum of control (n=4) and *Casp8*$^{\Delta IEC}$ (n=6) mice after TNF-treatment (+SEM, relative to *HPRT*) **(e)** Immunofluorescence staining of RIP3 in terminal ileum cross sections of TNF-treated *Casp8*$^{\Delta IEC}$ mice.



Suppl. Figure 9: Expression of *RIP1* and *RIP3* in the small intestine of control and *Casp8*$^{\Delta IEC}$ mice.
Quantitative RT-PCR analysis of *RIP* expression in unchallenged primary IEC of control (n=6) and *Casp8*$^{\Delta IEC}$ (n=6) mice (mean values relative to *HPRT* +SEM).

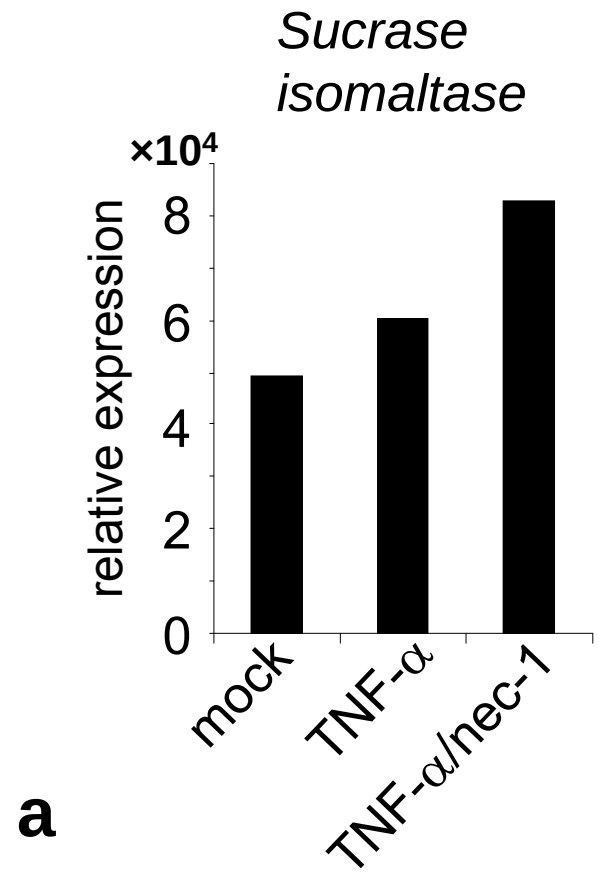


a

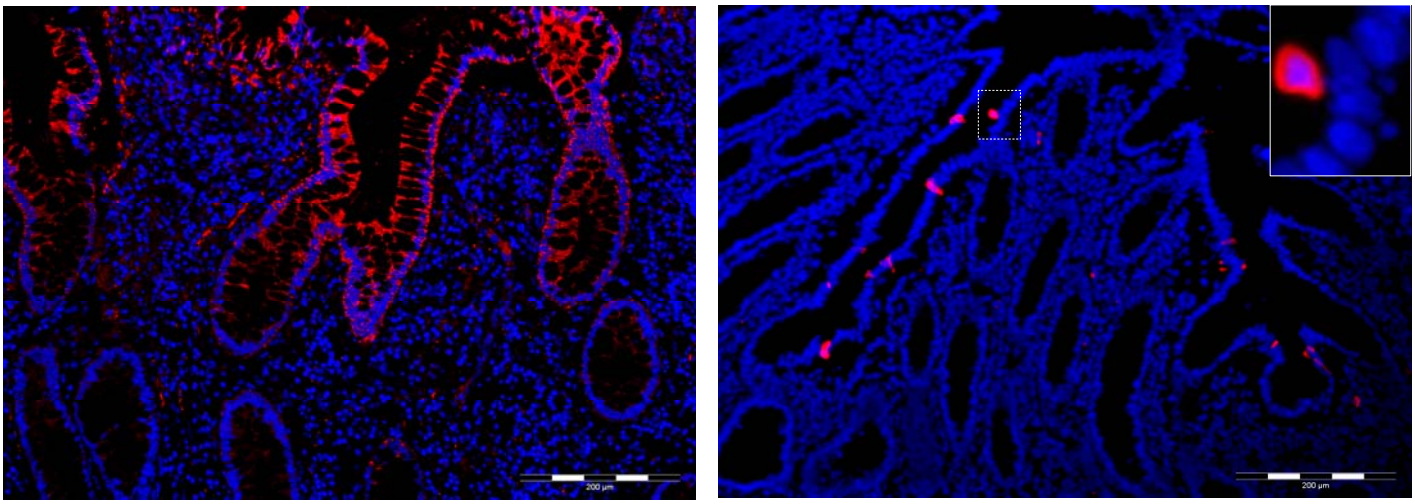


b

Suppl. Figure 10: TNF-α and RIP-3 expression in the small intestine.
(a) Quantitative expression level (n=3) of *TNF-α* and *RIP3* in bowel segments of healthy control mice. DD=duodenum, JJ=Jejunum, PI=proximal ileum, TI=terminal ileum, CO=colon (+SEM, relative to *HPRT*) **(b)** Immunofluorescence detection of TNF-α and RIP3 in small intestine cross sections of healthy control mice.



a



b caspase-8 cleaved caspase-8

Suppl. Figure 11: Caspase-8 expression in the human terminal ileum.
(a) GRAPHS: Quantitative expression level of the enterocyte marker *sucrase isomaltase* relative to *HPRT* in biopsies from the small intestine of control patients stimulated *in vitro* with either DMSO (mock), TNF-α alone or in combination with necrostatin-1. Data from one representative experiment out of 2 is shown. **(b)** Representative pictures of a cross section from the terminal ileum of a control patient stained for caspase-8 and activated caspase-8 (cleaved caspase-8).

List of genes downregulated in Casp8$^{\Delta IEC}$

Probeset	Gene Title	Gene Symbol	**fold change**	P-value
1436712_at	phospholipase A2, group IVC (cytosolic, calcium-independent)	Pla2g4c	**14,4**	0,0014
1438612_a_at	colipase, pancreatic	Clps	**12,0**	0,0000
1440832_at	angiogenin, ribonuclease A family, member 4	Ang4	**11,8**	0,0004
1415805_at	colipase, pancreatic	Clps	**10,2**	0,0000
1417735_at	RIKEN cDNA 1810030J14 gene	1810030J14Rik	**9,9**	0,0003
1438364_x_at	angiogenin, ribonuclease A family, member 4	Ang4	**8,9**	0,0001
1450788_at	serum amyloid A 1	Saa1	**7,9**	0,0813
1418368_at	resistin like beta	Retnlb	**7,0**	0,0788
1419075_s_at	serum amyloid A 1	Saa1	**6,9**	0,0832
1454883_at	gasdermin C2 /// hypothetical protein LOC100045250	Gsdmc2 /// LOC100045250	**6,1**	0,0016
1422242_at	defensin, alpha, related sequence 10	Defa-rs10	**5,7**	0,0012
1448595_a_at	brain expressed gene 1	Bex1	**5,7**	0,0174
1418171_at	similar to transcription elongation factor A (SII)-like 8 /// transcription elongi	LOC100045031 /// Tceal8	**5,4**	0,0198
1419665_a_at	nuclear protein 1	Nupr1	**5,4**	0,0010
1419294_at	RIKEN cDNA 1700011H14 gene	1700011H14Rik	**5,3**	0,0164
1418165_at	intelectin 1 (galactofuranose binding)	Itln1	**5,2**	0,0002
1428209_at	brain expressed gene 4	Bex4	**5,1**	0,0018
1430641_at	gasdermin C2 /// gasdermin C4	Gsdmc2 /// Gsdmc4	**5,1**	0,0009
1438858_x_at	histocompatibility 2, class II antigen A, alpha	H2-Aa	**4,9**	0,0034
1425519_a_at	CD74 antigen (invariant polypeptide of major histocompatibility complex, cl	Cd74	**4,8**	0,0042
1419591_at	gasdermin C	Gsdmc	**4,7**	0,0014
1419615_at	transient receptor potential cation channel, subfamily V, member 6	Trpv6	**4,6**	0,0175
1436857_at	defensin, alpha, 21 /// defensin, alpha, 22	Defa21 /// Defa22	**4,6**	0,0008
1419666_x_at	nuclear protein 1	Nupr1	**4,4**	0,0003
1429378_x_at	cDNA sequence AY761184	AY761184	**4,4**	0,0019
1443783_x_at	histocompatibility 2, class II antigen A, alpha	H2-Aa	**4,4**	0,0134
1448573_a_at	carcinoembryonic antigen-related cell adhesion molecule 10	Ceacam10	**4,3**	0,0013
1436242_a_at	chemokine-like factor	Cklf	**4,2**	0,0051
1420249_s_at	chemokine (C-C motif) ligand 6	Ccl6	**4,1**	0,0003
1435290_x_at	histocompatibility 2, class II antigen A, alpha	H2-Aa	**4,1**	0,0016
1428393_at	neuritin 1	Nrn1	**4,0**	0,0027
1449478_at	matrix metallopeptidase 7	Mmp7	**4,0**	0,0046
1417074_at	carcinoembryonic antigen-related cell adhesion molecule 10	Ceacam10	**3,9**	0,0031
1417266_at	chemokine (C-C motif) ligand 6	Ccl6	**3,9**	0,0001
1449580_s_at	histocompatibility 2, class II, locus Mb1 /// histocompatibility 2, class II, locu	H2-DMb1 /// H2-DMb2	**3,8**	0,0125
1422527_at	histocompatibility 2, class II, locus DMa	H2-DMa	**3,7**	0,0146
1450648_s_at	histocompatibility 2, class II antigen A, beta 1	H2-Ab1	**3,7**	0,0077
1451721_a_at	histocompatibility 2, class II antigen A, beta 1	H2-Ab1	**3,7**	0,0068
1450128_at	phospholipase A2, group IIA (platelets, synovial fluid)	Pla2g2a	**3,7**	0,0029
1429896_at	RIKEN cDNA 5830408B19 gene	5830408B19Rik	**3,6**	0,0007
1416490_at	transmembrane emp24 protein transport domain containing 6	Tmed6	**3,6**	0,0020
1424618_at	4-hydroxyphenylpyruvic acid dioxygenase	Hpd	**3,6**	0,0016
1437403_at	sterile alpha motif domain containing 5	Samd5	**3,6**	0,0001
1452431_s_at	histocompatibility 2, class II antigen A, alpha	H2-Aa	**3,5**	0,0018
1418638_at	histocompatibility 2, class II, locus Mb1 /// histocompatibility 2, class II, locu	H2-DMb1 /// H2-DMb2	**3,5**	0,0116
1459889_at	chloride channel calcium activated 3	Clca3	**3,5**	0,0081
1450709_at	defensin, alpha, 5 /// predicted gene 10104 /// predicted gene 15315	Defa5 /// Gm10104 /// Gm15315	**3,5**	0,0008
1456319_at	---	---	**3,4**	0,0918
1423547_at	lysozyme 2	Lyz2	**3,4**	0,0029
1418550_x_at	defensin, alpha, related sequence 1	Defa-rs1	**3,3**	0,0006
1437438_x_at	pancreatic lipase-related protein 2	Pnliprp2	**3,3**	0,0071
1450988_at	leucine rich repeat containing G protein coupled receptor 5	Lgr5	**3,2**	0,0054
1425477_x_at	histocompatibility 2, class II antigen A, beta 1	H2-Ab1	**3,2**	0,0038
1451791_at	tissue factor pathway inhibitor	Tfpi	**3,2**	0,0044
1417025_at	histocompatibility 2, class II antigen E beta	H2-Eb1	**3,2**	0,0087
1417872_at	four and a half LIM domains 1	Fhl1	**3,2**	0,0654
1421211_a_at	class II transactivator	Ciita	**3,2**	0,0115
1427351_s_at	immunoglobulin heavy chain 6 (heavy chain of IgM)	Igh-6	**3,1**	0,0449
1448021_at	family with sequence similarity 46, member C	Fam46c	**3,0**	0,0031
1438306_at	ring finger protein 180	Rnf180	**3,0**	0,0892
1450631_x_at	defensin, alpha, 24	Defa24	**3,0**	0,0002
1453317_a_at	KH domain containing, RNA binding, signal transduction associated 3	Khdrbs3	**3,0**	0,0154
1427482_a_at	carbonic anhydrase 8	Car8	**2,9**	0,0013
1436814_at	RIKEN cDNA 1810010D01 gene	1810010D01Rik	**2,9**	0,0001
1435387_at	solute carrier family 2 (facilitated glucose transporter), member 13	Slc2a13	**2,9**	0,0189
1448299_at	solute carrier family 1 (neuronal/epithelial high affinity glutamate transporte	Slc1a1	**2,9**	0,0069
1437263_at	RIKEN cDNA A730089K16 gene	A730089K16Rik	**2,9**	0,0223
1444668_at	amplified spermatogenic transcripts X encoded	Astx	**2,9**	0,0274
1441231_at	Predicted gene 3626	Gm3626	**2,8**	0,0129
1448186_at	pancreatic lipase-related protein 2	Pnliprp2	**2,8**	0,0269
1427054_s_at	ABI gene family, member 3 (NESH) binding protein	Abi3bp	**2,8**	0,0626
1443225_at	activin A receptor, type IC	Acvr1c	**2,7**	0,0069
1439426_x_at	lysozyme 1	Lyz1	**2,7**	0,0000
1437422_at	sema domain, seven thrombospondin repeats (type 1 and type 1-like), tran	Sema5a	**2,7**	0,0740
1418282_x_at	serine (or cysteine) preptidase inhibitor, clade A, member 1B	Serpina1b	**2,7**	0,0007
1439473_at	---	---	**2,7**	0,0422
1446748_at	RIKEN cDNA 2010007H06 gene	2010007H06Rik	**2,7**	0,0003
1459443_at	---	---	**2,7**	0,0116
1427344_s_at	RASD family, member 2	Rasd2	**2,7**	0,0062
1425415_a_at	solute carrier family 1 (neuronal/epithelial high affinity glutamate transporte	Slc1a1	**2,6**	0,0034
1438239_at	midline 1	Mid1	**2,6**	0,0505

1427063_at	RIKEN cDNA 5330417C22 gene	5330417C22Rik	**2,6**	0,0042
1428097_at	RIKEN cDNA 2510009E07 gene	2510009E07Rik	**2,6**	0,0395
1456789_at	zinc finger protein 462	Zfp462	**2,6**	0,0210
1420250_at	---	---	**2,6**	0,0066
1436996_x_at	lysozyme 1	Lyz1	**2,6**	0,0000
1437409_s_at	G protein-coupled receptor 126	Gpr126	**2,6**	0,0107
1442113_at	RIKEN cDNA 5330417C22 gene	5330417C22Rik	**2,5**	0,0004
1442537_at	---	---	**2,5**	0,0016
1418654_at	hydroxyacid oxidase 2	Hao2	**2,5**	0,0236
1423753_at	BMP and activin membrane-bound inhibitor, homolog (Xenopus laevis)	Bambi	**2,5**	0,0109
1448545_at	syndecan 2	Sdc2	**2,5**	0,0288
1457823_at	cysteine rich protein 61	Cyr61	**2,5**	0,0286
1449233_at	basic helix-loop-helix family, member a15	Bhlha15	**2,4**	0,0096
1445598_at	---	---	**2,4**	0,0713
1418925_at	cadherin, EGF LAG seven-pass G-type receptor 1 (flamingo homolog, Dro	Celsr1	**2,4**	0,0026
1424556_at	pyrroline-5-carboxylate reductase 1	Pycr1	**2,4**	0,0012
1417399_at	growth arrest specific 6	Gas6	**2,4**	0,0129
1446772_at	---	---	**2,4**	0,0116
1451513_x_at	serine (or cysteine) peptidase inhibitor, clade A, member 1A /// serine (or c	Serpina1a /// Serpina1b	**2,4**	0,0012
1450822_at	lysozyme 1	Lyz1	**2,4**	0,0000
1438385_s_at	glutamic pyruvate transaminase (alanine aminotransferase) 2	Gpt2	**2,3**	0,0074
1442340_x_at	cysteine rich protein 61	Cyr61	**2,3**	0,0281
1430479_at	RIKEN cDNA 2010007H06 gene	2010007H06Rik	**2,3**	0,0014
1457904_at	carbonic anhydrase 8	Car8	**2,3**	0,0017
1452317_at	homeobox B9	Hoxb9	**2,3**	0,0731
1449326_x_at	serum amyloid A 2	Saa2	**2,3**	0,0897
1415837_at	kallikrein 1	Klk1	**2,3**	0,0098
1417290_at	leucine-rich alpha-2-glycoprotein 1	Lrg1	**2,3**	0,0039
1436815_x_at	RIKEN cDNA 1810010D01 gene	1810010D01Rik	**2,3**	0,0005
1451230_a_at	WW domain binding protein 5	Wbp5	**2,3**	0,0006
1418780_at	cytochrome P450, family 39, subfamily a, polypeptide 1	Cyp39a1	**2,3**	0,0049
1433847_at	family with sequence similarity 40, member B	Fam40b	**2,3**	0,0324
1450781_at	high mobility group AT-hook 2	Hmga2	**2,3**	0,0049
1417011_at	syndecan 2	Sdc2	**2,3**	0,0557
1448107_x_at	kallikrein 1	Klk1	**2,3**	0,0110
1416306_at	chloride channel calcium activated 3	Clca3	**2,3**	0,0016
1418376_at	fibroblast growth factor 15	Fgf15	**2,3**	0,0250
1437385_at	collagen and calcium binding EGF domains 1	Ccbe1	**2,3**	0,0045
1443408_at	---	---	**2,3**	0,0007
1448680_at	similar to serine (or cysteine) proteinase inhibitor, clade A, member 1c /// s	LOC100046946 /// Serpina1c	**2,3**	0,0056
1427119_at	serine peptidase inhibitor, Kazal type 4	Spink4	**2,2**	0,0011
1428948_at	potassium large conductance calcium-activated channel, subfamily M, alpl	Kcnma1	**2,2**	0,0006
1450139_at	endoplasmic reticulum (ER) to nucleus signalling 2	Ern2	**2,2**	0,0018
1442447_at	---	---	**2,2**	0,0704
1448698_at	cyclin D1	Ccnd1	**2,2**	0,0465
1460359_at	armadillo repeat containing, X-linked 3	Armcx3	**2,2**	0,0996
1438244_at	nuclear factor I/B	Nfib	**2,2**	0,0176
1416473_a_at	immunoglobulin superfamily, DCC subclass, member 4	Igdcc4	**2,2**	0,0155
1460407_at	Spi-B transcription factor (Spi-1/PU.1 related)	Spib	**2,2**	0,0161
1452326_at	ATPase, Ca++ transporting, type 2C, member 2	Atp2c2	**2,2**	0,0014
1438245_at	---	---	**2,2**	0,0558
1439622_at	Ras association (RalGDS/AF-6) domain family member 4	Rassf4	**2,2**	0,0173
1449455_at	hemopoietic cell kinase	Hck	**2,2**	0,0183
1457483_at	---	---	**2,2**	0,0751
1456960_at	---	---	**2,2**	0,0837
1435367_at	mitogen-activated protein kinase 4	Mapk4	**2,2**	0,0796
1439106_at	zinc finger protein 462	Zfp462	**2,2**	0,0266
1460601_at	myosin VIIA and Rab interacting protein	Myrip	**2,2**	0,0003
1447174_at	---	---	**2,2**	0,0301
1425952_a_at	glucagon	Gcg	**2,2**	0,0049
1440285_at	protein phosphatase 1, regulatory (inhibitor) subunit 9A	Ppp1r9a	**2,2**	0,0221
1424271_at	doublecortin-like kinase 1	Dclk1	**2,1**	0,0121
1460386_a_at	solute carrier family 1 (neuronal/epithelial high affinity glutamate transporte	Slc1a1	**2,1**	0,0004
1417419_at	cyclin D1	Ccnd1	**2,1**	0,0481
1425182_x_at	kallikrein 1-related peptidase b22 /// kallikrein 1-related peptidase b9	Klk1b22 /// Klk1b9	**2,1**	0,0147
1447624_s_at	storkhead box 2	Stox2	**2,1**	0,0863
1445838_at	---	---	**2,1**	0,0101
1457664_x_at	complement component 2 (within H-2S)	C2	**2,1**	0,0027
1440770_at	B-cell leukemia/lymphoma 2	Bcl2	**2,1**	0,0898
1424373_at	armadillo repeat containing, X-linked 3	Armcx3	**2,1**	0,0044
1441727_s_at	zinc finger protein 467	Zfp467	**2,1**	0,0053
1460667_at	cDNA sequence U90926	U90926	**2,1**	0,0183
1428114_at	solute carrier family 14 (urea transporter), member 1	Slc14a1	**2,1**	0,0126
1437960_at	calpain 13	Capn13	**2,1**	0,0023
1433209_at	RIKEN cDNA 2210017G18 gene	2210017G18Rik	**2,1**	0,0190
1453234_at	RIKEN cDNA 1300002K09 gene	1300002K09Rik	**2,1**	0,0042
1424394_at	selenoprotein M	Selm	**2,1**	0,0003
1435078_at	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 2	Tanc2	**2,1**	0,0833
1424218_a_at	cAMP responsive element binding protein 3-like 4	Creb3l4	**2,1**	0,0061
1430804_at	solute carrier family 13 (sodium/sulfate symporters), member 1	Slc13a1	**2,1**	0,0079
1441482_at	---	---	**2,1**	0,0112
1434881_s_at	potassium channel tetramerisation domain containing 12	Kctd12	**2,1**	0,0364
1435939_s_at	HEPACAM family member 2	Hepacam2	**2,1**	0,0012
1416034_at	CD24a antigen	Cd24a	**2,1**	0,0330
1459253_at	RIKEN cDNA 1700023H06 gene	1700023H06Rik	**2,1**	0,0216

1451790_a_at	tissue factor pathway inhibitor	Tfpi	**2,1**	0,0204
1448182_a_at	CD24a antigen	Cd24a	**2,1**	0,0085
1443056_at	---	---	**2,1**	0,0869
1429831_at	phosphoinositide-3-kinase adaptor protein 1	Pik3ap1	**2,1**	0,0148
1451912_a_at	fibroblast growth factor receptor-like 1 /// similar to fibroblast growth factor	Fgfrl1 /// LOC100046239	**2,1**	0,0063
1443075_at	---	---	**2,1**	0,0614
1451498_at	leucine rich repeat containing 26	Lrrc26	**2,1**	0,0014
1456480_at	furry homolog (Drosophila)	Fry	**2,1**	0,0689
1428435_at	mucin 2	Muc2	**2,1**	0,0108
1447166_at	---	---	**2,0**	0,0213
1430357_at	H3 histone, family 3B	H3f3b	**2,0**	0,0330
1415777_at	pancreatic lipase related protein 1	Pnliprp1	**2,0**	0,0347
1451289_at	doublecortin-like kinase 1	Dclk1	**2,0**	0,0084
1424439_at	RIKEN cDNA 1810065E05 gene	1810065E05Rik	**2,0**	0,0238
1456072_at	protein phosphatase 1, regulatory (inhibitor) subunit 9A	Ppp1r9a	**2,0**	0,0193
1449464_at	potassium voltage-gated channel, subfamily Q, member 1	Kcnq1	**2,0**	0,0138
1418355_at	nucleobindin 2	Nucb2	**2,0**	0,0048
1419086_at	fibroblast growth factor binding protein 1	Fgfbp1	**2,0**	0,0191
1417420_at	cyclin D1	Ccnd1	**2,0**	0,0206
1417985_at	Notch-regulated ankyrin repeat protein	Nrarp	**2,0**	0,0143
1452966_at	B-cell leukemia/lymphoma 11B	Bcl11b	**2,0**	0,0697
1426990_at	cubilin (intrinsic factor-cobalamin receptor)	Cubn	**2,0**	0,0511
1446095_at	antisense Igf2r RNA	Airn	**2,0**	0,0676
1441644_at	---	---	**2,0**	0,0517
1441498_at	---	---	**2,0**	0,0712
1441375_at	---	---	**2,0**	0,0873
1445881_at	RIKEN cDNA 2310035P21 gene	2310035P21Rik	**2,0**	0,0411
1422422_at	defensin, alpha, 4	Defa4	**2,0**	0,0030
1420822_s_at	sphingosine-1-phosphate phosphatase 1	Sgpp1	**2,0**	0,0018

List of genes upregulated in Casp8$^{\Delta IEC}$

Probeset	Gene Title	Gene Symbol	**fold change**	P-value
1451798_at	interleukin 1 receptor antagonist	Il1rn	**9,6**	0,0012
1453092_at	cysteine-rich C-terminal 1	Crct1	**8,3**	0,0002
1448213_at	annexin A1	Anxa1	**7,8**	0,0039
1427873_at	defensin, alpha, 15	Defa15	**6,5**	0,0000
1422749_at	lymphocyte antigen 6 complex, locus G6C	Ly6g6c	**6,1**	0,0149
1451612_at	metallothionein 1	Mt1	**5,8**	0,0007
1416930_at	lymphocyte antigen 6 complex, locus D	Ly6d	**5,7**	0,0067
1427760_s_at	prolactin family 2, subfamily c, member 2 /// prolactin family 2, subfamily c	Prl2c2 /// Prl2c3 /// Prl2c4	**5,5**	0,0002
1425663_at	interleukin 1 receptor antagonist	Il1rn	**4,9**	0,0016
1427735_a_at	actin, alpha 1, skeletal muscle	Acta1	**4,4**	0,0034
1423436_at	glutathione S-transferase, alpha 3	Gsta3	**4,3**	0,0053
1428958_at	progestin and adipoQ receptor family member VIII	Paqr8	**4,0**	0,0064
1422008_a_at	aquaporin 3	Aqp3	**3,7**	0,0096
1444468_at	progestin and adipoQ receptor family member VIII	Paqr8	**3,5**	0,0004
1435246_at	progestin and adipoQ receptor family member VIII	Paqr8	**3,4**	0,0005
1422400_a_at	GPI anchored molecule like protein /// hematopoietic cell transcript 1	Gml /// Hemt1	**3,4**	0,0820
1419717_at	sema domain, immunoglobulin domain (Ig), short basic domain, secreted,	Sema3e	**3,4**	0,0001
1449133_at	small proline-rich protein 1A	Sprr1a	**3,3**	0,0870
1421008_at	radical S-adenosyl methionine domain containing 2	Rsad2	**3,3**	0,0807
1421040_a_at	glutathione S-transferase, alpha 2 (Yc2)	Gsta2	**3,3**	0,0123
1448894_at	aldo-keto reductase family 1, member B8	Akr1b8	**3,2**	0,0107
1422639_at	calcitonin-related polypeptide, beta	Calcb	**3,2**	0,0147
1421923_at	SH3-domain binding protein 5 (BTK-associated)	Sh3bp5	**3,2**	0,0081
1427912_at	carbonyl reductase 3	Cbr3	**3,2**	0,0100
1424962_at	transmembrane 4 superfamily member 4	Tm4sf4	**3,2**	0,0039
1425567_a_at	annexin A5	Anxa5	**3,1**	0,0011
1423437_at	glutathione S-transferase, alpha 3	Gsta3	**3,1**	0,0005
1422557_s_at	metallothionein 1	Mt1	**3,1**	0,0001
1431042_at	progestin and adipoQ receptor family member VIII	Paqr8	**2,9**	0,0015
1421752_a_at	serine (or cysteine) peptidase inhibitor, clade B, member 5	Serpinb5	**2,9**	0,0523
1422620_s_at	phosphatidic acid phosphatase type 2A	Ppap2a	**2,9**	0,0009
1441851_x_at	lymphocyte antigen 6 complex, locus G6C	Ly6g6c	**2,9**	0,0288
1431591_s_at	predicted gene 9706 /// ISG15 ubiquitin-like modifier	Gm9706 /// Isg15	**2,8**	0,0046
1449385_at	hydroxysteroid (17-beta) dehydrogenase 6	Hsd17b6	**2,8**	0,0093
1421134_at	amphiregulin	Areg	**2,8**	0,0171
1449195_s_at	chemokine (C-X-C motif) ligand 16	Cxcl16	**2,8**	0,0007
1422619_at	phosphatidic acid phosphatase type 2A	Ppap2a	**2,8**	0,0007
1421912_at	solute carrier family 23 (nucleobase transporters), member 1	Slc23a1	**2,8**	0,0351
1459059_at	RIKEN cDNA 2010308F09 gene	2010308F09Rik	**2,7**	0,0336
1417889_at	apolipoprotein B mRNA editing enzyme, catalytic polypeptide 2	Apobec2	**2,6**	0,0608
1451777_at	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60	Ddx60	**2,6**	0,0114
1420499_at	GTP cyclohydrolase 1	Gch1	**2,6**	0,0105
1450404_at	solute carrier family 23 (nucleobase transporters), member 1	Slc23a1	**2,6**	0,0188
1419816_s_at	ERBB receptor feedback inhibitor 1	Errfi1	**2,5**	0,0269
1430674_at	RIKEN cDNA 1700016C15 gene	1700016C15Rik	**2,5**	0,0419
1418572_x_at	tumor necrosis factor receptor superfamily, member 12a	Tnfrsf12a	**2,5**	0,0192
1416257_at	calpain 2	Capn2	**2,5**	0,0143
1443841_x_at	UDP-N-acteylglucosamine pyrophosphorylase 1-like 1	Uap1l1	**2,5**	0,0011
1438037_at	hect domain and RLD 5	Herc5	**2,5**	0,0088
1422975_at	membrane metallo endopeptidase	Mme	**2,5**	0,0309
1432282_a_at	TLC domain containing 2	Tlcd2	**2,5**	0,0081
1438036_x_at	family with sequence similarity 82, member A1	Fam82a1	**2,5**	0,0699
1428834_at	dual specificity phosphatase 4	Dusp4	**2,5**	0,0118
1424853_s_at	cytochrome P450, family 4, subfamily a, polypeptide 10 /// cytochrome P4	Cyp4a10 /// Cyp4a31	**2,4**	0,0238
1449071_at	myosin, light polypeptide 7, regulatory	Myl7	**2,4**	0,0470
1438579_at	UTP14, U3 small nucleolar ribonucleoprotein, homolog B (yeast)	Utp14b	**2,4**	0,0296
1428386_at	acyl-CoA synthetase long-chain family member 3	Acsl3	**2,4**	0,0070
1423555_a_at	interferon-induced protein 44	Ifi44	**2,4**	0,0212
1416200_at	interleukin 33	Il33	**2,4**	0,0561
1418571_at	tumor necrosis factor receptor superfamily, member 12a	Tnfrsf12a	**2,4**	0,0285
1424339_at	2'-5' oligoadenylate synthetase-like 1	Oasl1	**2,4**	0,0166
1450460_at	aquaporin 3	Aqp3	**2,4**	0,0076
1447243_at	cDNA sequence BC040756	BC040756	**2,4**	0,0196
1419207_at	zinc finger protein 37	Zfp37	**2,4**	0,0235
1449789_x_at	lymphocyte antigen 6 complex, locus G6C	Ly6g6c	**2,4**	0,0751
1455063_at	family with sequence similarity 82, member A1	Fam82a1	**2,4**	0,0144
1424623_at	serine (or cysteine) peptidase inhibitor, clade B, member 5	Serpinb5	**2,3**	0,0015
1449025_at	interferon-induced protein with tetratricopeptide repeats 3	Ifit3	**2,3**	0,0049
1417311_at	cysteine rich protein 2	Crip2	**2,3**	0,0431
1452771_s_at	acyl-CoA synthetase long-chain family member 3	Acsl3	**2,3**	0,0176
1455106_a_at	creatine kinase, brain	Ckb	**2,3**	0,0038
1421073_a_at	prostaglandin E receptor 4 (subtype EP4)	Ptger4	**2,3**	0,0357
1425137_a_at	histocompatibility 2, Q region locus 10	H2-Q10	**2,3**	0,0490
1434028_at	aryl hydrocarbon receptor nuclear translocator 2	Arnt2	**2,3**	0,0074
1422072_a_at	glutathione S-transferase, mu 6	Gstm6	**2,3**	0,0102
1422007_at	aquaporin 3	Aqp3	**2,3**	0,0028
1456178_at	BMP and activin membrane-bound inhibitor, pseudogene (Xenopus laevis	Bambi-ps1	**2,3**	0,0039
1424295_at	developmental pluripotency-associated 3	Dppa3	**2,3**	0,0408
1418718_at	chemokine (C-X-C motif) ligand 16	Cxcl16	**2,3**	0,0024
1434130_at	lipoma HMGIC fusion partner-like 2	Lhfpl2	**2,3**	0,0604
1418098_at	adenylate cyclase 4	Adcy4	**2,3**	0,0045
1435323_a_at	membrane bound O-acyltransferase domain containing 1	Mboat1	**2,3**	0,0029

1450355_a_at	capping protein (actin filament), gelsolin-like	Capg	**2,2**	0,0180
1427303_at	ectonucleotide pyrophosphatase/phosphodiesterase 3	Enpp3	**2,2**	0,0215
1418580_at	receptor transporter protein 4	Rtp4	**2,2**	0,0025
1419576_at	homeobox B13	Hoxb13	**2,2**	0,0200
1424268_at	spermine oxidase	Smox	**2,2**	0,0083
1451794_at	transmembrane and coiled coil domains 3	Tmcc3	**2,2**	0,0922
1456288_at	schlafen 5	Slfn5	**2,2**	0,0254
1447861_x_at	Meis homeobox 2	Meis2	**2,2**	0,0809
1439114_at	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60	Ddx60	**2,2**	0,0239
1451775_s_at	interleukin 13 receptor, alpha 1	Il13ra1	**2,2**	0,0077
1431095_a_at	hect domain and RLD 5	Herc5	**2,2**	0,0348
1453939_x_at	predicted gene 9706	Gm9706	**2,2**	0,0506
1455423_at	KH domain containing 1A	Khdc1a	**2,2**	0,0302
1446406_at	---	---	**2,2**	0,0364
1422757_at	solute carrier family 5 (neutral amino acid transporters, system A), membe	Slc5a4b	**2,1**	0,0123
1427885_at	polymerase (DNA-directed), delta 4	Pold4	**2,1**	0,0278
1432260_at	G protein-coupled receptor 39	Gpr39	**2,1**	0,0007
1423933_a_at	RIKEN cDNA 1600029D21 gene	1600029D21Rik	**2,1**	0,0769
1456784_at	predicted gene 14137	Gm14137	**2,1**	0,0196
1438856_x_at	serine (or cysteine) peptidase inhibitor, clade B, member 5	Serpinb5	**2,1**	0,0486
1449453_at	bone marrow stromal cell antigen 1	Bst1	**2,1**	0,0073
1460330_at	annexin A3	Anxa3	**2,1**	0,0086
1441941_x_at	serine (or cysteine) peptidase inhibitor, clade B, member 5	Serpinb5	**2,1**	0,0378
1451516_at	Ras homolog enriched in brain like 1	Rhebl1	**2,1**	0,0363
1444270_at	radial spoke head 4 homolog A (Chlamydomonas)	Rsph4a	**2,1**	0,0015
1453757_at	hect domain and RLD 5	Herc5	**2,1**	0,0093
1436417_at	solute carrier family 19 (sodium/hydrogen exchanger), member 3	Slc19a3	**2,1**	0,0231
1450430_at	mannose receptor, C type 1	Mrc1	**2,1**	0,0051
1420931_at	mitogen-activated protein kinase 8	Mapk8	**2,1**	0,0180
1446509_at	spermine oxidase	Smox	**2,1**	0,0125
1457632_s_at	Meis homeobox 2	Meis2	**2,1**	0,0889
1423017_a_at	interleukin 1 receptor antagonist	Il1rn	**2,1**	0,0056
1430172_a_at	cytochrome P450, family 4, subfamily f, polypeptide 16 /// predicted gene	Cyp4f16 /// Gm9705	**2,1**	0,0140
1424265_at	N-acetylneuraminate pyruvate lyase	Npl	**2,1**	0,0178
1421096_at	transient receptor potential cation channel, subfamily C, member 1	Trpc1	**2,1**	0,0510
1432374_a_at	ethanolaminephosphotransferase 1 (CDP-ethanolamine-specific)	Ept1	**2,1**	0,0216
1437161_x_at	RNA binding protein gene with multiple splicing	Rbpms	**2,1**	0,0691
1417837_at	pleckstrin homology-like domain, family A, member 2	Phlda2	**2,1**	0,0065
1448813_at	arylacetamide deacetylase (esterase)	Aadac	**2,1**	0,0345
1418069_at	apolipoprotein C-II	Apoc2	**2,1**	0,0041
1453590_at	ADP-ribosylation factor-like 5B	Arl5b	**2,1**	0,0861
1421011_at	hydroxysteroid (17-beta) dehydrogenase 11	Hsd17b11	**2,1**	0,0003
1450783_at	interferon-induced protein with tetratricopeptide repeats 1	Ifit1	**2,1**	0,0329
1451755_a_at	apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1	Apobec1	**2,1**	0,0192
1427302_at	ectonucleotide pyrophosphatase/phosphodiesterase 3	Enpp3	**2,1**	0,0071
1432453_a_at	membrane-spanning 4-domains, subfamily A, member 10	Ms4a10	**2,1**	0,0188
1424592_a_at	deoxyribonuclease I	Dnase1	**2,0**	0,0066
1422846_at	retinol binding protein 2, cellular	Rbp2	**2,0**	0,0089
1421078_at	transcription factor 23	Tcf23	**2,0**	0,0681
1416165_at	RAB31, member RAS oncogene family	Rab31	**2,0**	0,0018
1438606_a_at	chloride intracellular channel 4 (mitochondrial)	Clic4	**2,0**	0,0300
1456603_at	family with sequence similarity 101, member B	Fam101b	**2,0**	0,0002
1419395_at	acyl-CoA thioesterase 12	Acot12	**2,0**	0,0270
1428271_at	acyl-Coenzyme A binding domain containing 4	Acbd4	**2,0**	0,0153

Suppl. Table 1: Differential gene expression in IEC from control and Casp8ΔIEC mice.List of genes differentially expressed between IEC of control (n=3) and Casp8ΔIEC (n=3) mice. Gene chip data was analyzed as described in methods. Only genes with a fold change in expression > 2.0 and a p-value of < 0.05 are shown.