Supplementary Table 1. Comparison of disease phenotype between full body and intestinal epithelial-specific K8 knockout mouse models.

	Keratin 8 knockout mouse models			
	Full K8 knockouts (FVB/n background)*	Intestinal epithelial cell K8 knockouts (C57BL/6 background)**		
Disease phenotype	**$K8^{-/-}$**	**$K8^{flox/flox}$;Villin-$CreER^{t2}$*** **	**$K8^{flox/flox}$;Villin-Cre**	**References**
Colon inflammation	Yes, early onset	n.d.	Yes, in aging mice	Habtezion et al., 2005; Toivola et al., 2004 Asghar et al., 2014
Colonic epithelial hyperproliferation and increased crypt length	Yes	Yes	Yes	Baribault et al. 1994; Toivola et al., 2004
Cryptless/damaged areas	Yes	Yes	Yes	Asghar et al., 2015
Intestinal barrier compromised	Yes	n.d.	Yes	Misiorek et al., 2016
Diarrhea	Yes	Yes	Yes	Toivola et al., 2004
Enhanced colorectal cancer susceptibility	Yes	n.d.	Yes	Misiorek et al., 2016
Rectal prolapse	Observed	none	Observed	Baribault et al. 1994
Defects in other epithelial organs	Yes	n.d.	none	Tao et al., 2003; Jaquemar et al., 2003; Mathew et al., 2013; Alam et al., 2013; Odaka et al. 2013; Silvander et al. 2017
Embryo lethality	50 %	none	none	Baribault et al. 1994
Female infetitility	Yes	none	none	Baribault et al. 1994

*C57Bl/6, $K8^{-/-}$ mice are 95% embryo lethal with 100% female infertility (Baribault et al. 1993); **results from this study; ***25 days after tamoxifen treatment; n.d. not determined

Supplementary Table 2. Summary of K8 dependet cellular a+C4:G19nd molecular phenotypes in the colonic epithelium and serum of full body and the intestinal epithelium specific K8 knockout mouse				
Molecular phenotype		**Keratin 8 knockout mouse models**		
		Full K8 knockouts (FVB/n background)	**Intestinal epithelial cell K8 knockouts (C57BL/6 background)**	
		$K8^{-/-}$	**$K8^{flox/flox}$;Villin-Cre**	**References**
Simple epithelial keratins	**K7**	↓	↓*	Asghar et al., 2015; Figure 1
	K18	↓	↓*	
	K19	↓	↓*	
	K20	↓	↓*	
Cell proliferation and tissue repair	**IL-22**	↑	↑	Misiorek et al., 2016; Figure 5; Supplemental Figure 6
	IL-22BP	↓	↓*	
	p-STAT3	↑	↑*	
	p-pRb	↑	↑	Unpublished; Figure 5
Cell differentiation/ fate	**Goblet cells**	↑	↑	Lähdeniemi et al., 2017; Figure 5; Supplemental Figure 6
	Villin	↓	↓	
	Notch1	↓	↓*	
Energy metabolism	**HMGSC2**	↓	↓	Helenius et al., 2015; Unpublished
Serum cytokines	**IL-1β**	↑	↑	Supplemental Figure 5
	IL-5	↑	n.s	
	IL-6	↑	n.s	
	IL-18	↓	↓**	
	IL-22	↑	n.s	
	IFNγ	n.s	n.s	
	CCL-2	n.s	n.s	
	TNFα	n.s	n.s	

↑ indicates statistically significant increase and ↓ statistically significant decrease compared to respective K8 wild-type control mice; n.s. means non significant change, *$K8^{flox/flox}$;Villin-$CreER^{t2}$ show similar results, ** in aging mice.

Supplementary Table 3. List of primary and secondary antibodies used for western-blot analyses and immunofluorescence

Antibody name	Dilution	Company
Rabbit anti-K7	1:1000/1:100*	Abcam, Cambridge, UK (181598)
Rat anti-K8	1:1000/1:1000*	Developmental Studies Hybridoma Bank, IA, USA (troma I)
Rabbit anti-K18	1:1000/1:1000*	Kind gift from John Eriksson lab
Rat anti-K19	1:1000/1:1000*	EMD Millipore Corporation, CA, USA (MABT913)
Rabbit anti-K20	1:1000	Abcam, Cambridge, UK (97511)
Rabbit anti-Mu2	1:1000	Abcam, Cambridge, UK (272692)
Rabbit anti-Villin	1:1000	Invitrogen, Thermo Fisher Scientific, CA, USA (PA517290)
Rabbit anti-pRb	1:1000	Abcam, Cambridge, UK (181616)
Rabbit anti-pospho-pRb (ser807/811)	1:1000	Cell Signaling, MA, USA (8516)
Rabbit anti-full length Notch 1	1:1000	Cell Signaling, MA, USA (D1E11)
rabbit anti-cleaved Notch 1 (Val1744)	1:1000	Cell Signaling, MA, USA (D3B8)
Rabbit anti-full length Notch 1 (C-20)	1:1000	Santa Cruz, TX, USA (sc-6014)
Mouse anti-STAT3	1:1000	Cell Signaling, MA, USA (9139)
Rabbit anti-phospho-STAT3 (tyr705)	1:1000	Cell Signaling, MA, USA (9145)
Sheep anti-IL-22BP	1:1000	R&D systems (AF2376)
Rat anti-Hsc70	1:1000	Stressgen Bioreagents, MI, USA (SPA-815B)

*dilution factor applied for immunostainings

Supplementary Table 4. List of secondary antibodies used for western-blot analyses and immunofluorescence

Antibody name	Dilution	Company
Anti-rabbit Alexa Fluor 488/680**/800**	1:10000/1:200*	Invitrogen, CA, USA (A21206/A32734/A32735)
Anti-rat Alexa Fluor 488/568/680**	1:10000/1:200*	Invitrogen, CA, USA (A21208/A11077/A21096)
Anti-rabbit IgG-HRP	1:10000	Promega, WI, USA (W401B)
Anti-rat IgG-HRP	1:10000	Cell signaling, MA, USA (7077S)
Anti-mouse IgG-HRP	1:10000	GE Healthcare, UK (NA931V)
Anti-sheep IgG-HRP	1:10000	Sigma-Aldrich, MO, USA (12-342)

*dilution factor applied for immunostainings

**secondary only used for western-blot analyses

Supplemental Table 5. Primer sequences used for TaqMan and SYBR Green used for qRT-PCR gene expression analysis

Gene	Primer sequence	
	Forward primer	**Reverse primer**
18S rRNA	5'-GCA ATT ATT CCC CAT GAA CG -3'	5'-GGG ACT TAA TCA ACG CAA GC -3'
Actb	5'-TGG CTC CTA GCA CCA TGA AGA-3'	5'-GTG GAC AGT GAG GCC AGG AT-3'
Krt7	5'-GGA GAT GGC CAA CCA CAG-3'	5'-GGC CTG GAG TGT CTC AAA CTT-3'
Krt8	5'-TGA ATT TGT CCT CAT CAA GAA GG-3'	5'-GGA TCT CCT CTT CAT GGA TCT G-3'
Krt18	5'-AGA TGA CAC CAA CAT CAT CAC AAG G-3'	5'-CTT CCA GAC CTT GGA CTT CCT-3'
Krt19	5'-TGA CCT GGA GAT GCA GAT TG-3'	5'-CCT CAG GGC AGT AAT TTC CTC-3'
Krt20	5'-AGC TGA GAC GCA CCT ACC AG-3'	5'-TGC GCT CCA GAG ACT CTT TC-3'
Krt23	5'-TCA TGA AGA AAC GCC ATG AG-3'	5'-CCT TGA AGT CAC TCG GCA AG-3'
S100a11	5’-GGG AAG GAT GGA AAC AAC ACT-3’	5’-CAC CAG GAT CCT TCT GGT TC-3’
Plk1	5’-GCA GCA GGA AAC CTC TCA A-3’	5’-GCT GTA GCA AGT CAC TAA GGT-3’
Mybl2	5’-GCT GAT GTC CTC TAC CAT GC-3’	5’-CTG TTA CCC TCT TTG CTA CCT G-3’
Cdk1	5’-GAC TAC AAG AAC ACC TTT CCC A-3’	5’-CGT TTG GCA GGA TCA TAG ACT-3’
Ccnb1	5’-GCC TAT ATT GCA TTT CCT AGT GTG-3’	5’GAA TGA AGC CAA GCA AGA CAT-3’

Supplemental Table 6. TaqMan Gene Expression Assays used for qRT-PCR gene expression analysis

Gene	Expression Assay#
Bact	Mm02619580_g1
Ccl2	Mm00441242_m1
Mpo	Mm01298424_m1
Il18	Mm00434226_m1
Il22	Mm01226722_g1
Il4	Mm00445259_m1
Il6	Mm00446190_m1
Il1b	Mm00434228_m1