

**Supplemental Table S1.** Antibodies used in flow cytometry

Antibody	Format	Research Resource Identifiers (RRIDs)	Source
<b>Anti-human</b>			
ALDH1		RRID:AB_2784960	Thermo Fisher Scientific, Waltham, MA, USA
CD24	PerCP-Vio700	RRID:AB_2656568	Miltenyi Biotec, Bergisch Gladbach, Germany
CD26	PE	RRID:AB_2889525	“
CD44	APC	RRID:AB_398683	BD Biosciences, Franklin Lakes, NJ, USA
CD126	PE	RRID:AB_868803	“
CD130	FITC	RRID:AB_868803	Abcam, Cambridge, UK
CD133	PE	RRID:AB_2726287	Miltenyi Biotec, Bergisch Gladbach, Germany
CD166	APC	RRID:AB_2751830	“
CXCR3	APC	RRID:AB_398481	BD Biosciences, Franklin Lakes, NJ, USA
CXCR4		RRID:AB_2089399	R&D Systems, Minneapolis, MN, USA
EGFR	APC	RRID:AB_2651599	Miltenyi Biotec, Bergisch Gladbach, Germany
EpCAM	PerCP-Cy5.5	RRID:AB_400263	BD Biosciences, Franklin Lakes, NJ, USA
EPOR	PE	RRID:AB_2262227	R&D Systems, Minneapolis, MN, USA
IGFR1	APC	RRID:AB_1907365	Thermo Fisher Scientific, Waltham, MA, USA
IL30	eFluor 660	RRID:AB_11149127	“
Ki67	APC	RRID:AB_2688057	“
TIE2	PE	RRID:AB_2904809	Miltenyi Biotec, Bergisch Gladbach, Germany
VEGFR1	APC	RRID:AB_2784492	“
VEGFR2	PE	RRID:AB_2733728	“

**Supplemental Table S2.** Antibodies used in immunostaining

<b>Antibody</b>	<b>Clone</b>	<b>Origin</b>	<b>Research Resource Identifiers (RRIDs)</b>	<b>Source</b>
<b><i>Anti-human</i></b>				
CD14	7	Mouse	RRID:AB_563494	Leica Biosystems, Newcastle upon Tyne, UK
CD68	KP1	Mouse	RRID:AB_11151139	Thermo Fisher Scientific, Waltham, MA, USA
CXCL5	33160	Mouse	RRID:AB_2261181	R&D Systems, Minneapolis, MN, USA
CXCR4	44716	Mouse	RRID:AB_2089399	"
EGF	Z-12	Rabbit	RRID:AB_631417	Santa Cruz Biotechnology, Dallas, TX, USA
IGF1		Rabbit	RRID:AB_308724	Abcam, Cambridge, UK
IL30		Rabbit	RRID:AB_10898806	"
JAK1	6G4	Rabbit	RRID:AB_2265054	Cell Signaling Technology, Danvers, MA, USA
Ki67	MIB1	Mouse	RRID:AB_2142367	Agilent, Santa Clara, CA, USA
LYVE1		Rabbit	RRID:AB_535926	Novus Biologicals, Centennial, CO, USA
RARB		Rabbit	RRID:AB_11021140	"
STAT3	124H6	Mouse	RRID:AB_331757	Cell Signaling Technology, Danvers, MA, USA
TGFβ1	TB21	Mouse	RRID:AB_2539407	Thermo Fisher Scientific, Waltham, MA, USA
TNFα	1E8-G6	Mouse		Santa Cruz Biotechnology, Dallas, TX, USA
VEGFA	VG-1	Mouse	RRID:AB_299738	Abcam, Cambridge, UK
<b><i>Anti-mouse</i></b>				
CD31	SZ31	Rat	RRID:AB_2631039	Dianova, Hamburg, Germany
F4/80	Cl:A3-1	Rat	RRID:AB_323279	Bio-Rad, Hercules, CA, USA
IL30		Goat	RRID: AB_355012	R&D Systems, Minneapolis, MN, USA
Ly-6G	1A8	Rat	RRID:AB_1089179	BioLegend, San Diego, CA, USA

**Supplemental Table S3.** Clinicopathological characteristics of CRC patients included in the “*Colorectal Adenocarcinoma TCGA Nature 2012*” collection and IL30 gene expression in their tumor samples

	Number of patients	Percentages	IL30 gene expression	
			<i>IL30<sup>High</sup></i>	<i>IL30<sup>Mod</sup></i>
<b>Sex</b>				
Female	117	48.35%	6 (5.13%)	111 (94.87%)
Male	125	51.65%	6 (4.80%)	119 (95.20%)
<i>Total</i>	<i>242</i>	<i>100.00%</i>	<i>12 (4.96%)</i>	<i>230 (95.04%)</i>
<b>Age</b>				
≤40	3	1.24%	0 (0.00%)	3 (100.00%)
41-50	18	7.44%	1 (5.56%)	17 (94.44%)
51-60	26	10.74%	1 (3.85%)	25 (96.15%)
61-70	70	28.93%	4 (5.71%)	66 (94.29%)
71-80	69	28.51%	3 (4.35%)	66 (95.65%)
≥81	38	15.70%	2 (5.26%)	36 (94.74%)
UN*	18	7.44%	1 (5.56%)	17 (94.44%)
<i>Total</i>	<i>242</i>	<i>100.00%</i>	<i>12 (4.96%)</i>	<i>230 (95.04%)</i>
<b>Clinical Stage</b>				
Stage I	49	20.25%	2 (4.08%)	47 (95.92%)
Stage II	89	36.78%	5 (5.62%)	84 (94.38%)
Stage III	61	25.20%	3 (4.92%)	58 (95.08%)
Stage IV	40	16.53%	2 (5.00%)	38 (95.00%)
UN*	3	1.24%	0 (0.00%)	3 (100.00%)
<i>Total</i>	<i>242</i>	<i>100.00%</i>	<i>12 (4.96%)</i>	<i>230 (95.04%)</i>
<b>Molecular Subtype</b>				
CIN <sup>†</sup>	80	33.06%	4 (5.00%)	76 (95.00%)
MSI <sup>‡</sup>	68	28.10%	5 (7.35%)	63 (92.65%)
Invasive	57	23.55%	3 (5.26%)	54 (94.74%)
UN*	37	15.29%	0 (0.00%)	37 (100.00%)
<i>Total</i>	<i>242</i>	<i>100.00%</i>	<i>12 (4.96%)</i>	<i>230 (95.04%)</i>

\*Unavailable data.

†Chromosomal instability.

‡Microsatellite instability.

**Supplemental Table S4.** Changes in gene expression profile of CRC cells and CR-CSCs after IL30 gene deletion by CRISPR/Cas9 editing

Gene	CRC*	CR-CSC*
ZNF20	-418.00	-420.98 <sup>§</sup>
VEGFA	-418.10	-412.10
COL24A1	-172.81	-163.81
RAB33A	-99.81	-93.81
COL5A3	-64.52	-74.52
WNT5A	-12.10	-74.20
LYVE1	-60.19	-67.19
ADAM20	-57.98	-62.98
ZNF541	-55.02	-55.02
WNT8B	-52.59	-46.59
ANGPT2	-32.70	-39.70
NOS2	-39.70	-39.70
COL9A1	-34.93	-36.63
CXCL10	-26.89	-35.89
MMP21	-14.23	-31.94
ZNF429	-18.25	-28.25
CCR7	-33.77	-27.77
IL32	-27.14	-27.14
IGF1	-180.16	-24.49
ZNF157	-14.30	-24.30
MMP2	-15.00	-24.30
MUC8	-18.98	-23.98
PROM2	-33.53	-23.53
EGF	-16.20	-23.00
ZNF781	-10.65	-20.65
KLF18	-18.46	-20.46
EPO	-20.37	-20.37
CXCL11	-30.37	-20.37
TNR	-21.13	-20.18
CCR3	-24.69	-16.69
OSM	-11.69	-16.69
ZNF671	-21.69	-16.69
ZNF300	-9.69	-16.69
CCND2	-24.37	-16.37
ZNF287	-25.77	-16.37
ZNF578	-9.37	-16.37
CXCR4	-5.99	-15.15
MMP19	-2.10	-14.98
WNT3A	-4.60	-13.72
TNFSF10	-13.18	-13.18
IL13	-13.74	-13.05
ADAM33	-11.74	-13.05
RAB3C	-7.74	-13.05
ZNF521	-4.74	-13.05
MMP13	-5.20	-13.00

Gene	CRC*	CR-CSC*
SERPINI2	-9.35	-12.55
ZNF836	-7.76	-12.55
MMP9	-2.70	-12.50
ZNF608	-2.49	-11.49
WNT2	-5.80	-10.80
WNT4	-2.20	-9.73
FGF12	-5.81	-8.81
LTB	-2.19	-8.81
SEMA6D	-3.22	-8.81
WNT11	-2.80	-8.80
ALK	-8.72	-8.72
CCR1	-3.75	-8.72
CCL20	-17.72	-8.72
TNF	-2.77	-8.72
VTN	-15.72	-8.72
ADAM7	-4.32	-8.72
MUC15	-7.82	-8.72
CXCL17	-14.24	-8.72
NRG1	-17.72	-8.72
MUC6	-3.28	-8.72
SERPINA5	-9.08	-8.72
TRIB3	-5.60	-8.50
CXCL5	-2.57	-7.27
CXCR1	-2.50	-7.26
IL37	-15.03	-7.03
STAT3	-2.37	-6.72
CXCR2	-14.38	-6.38
JAK1	-5.70	-5.60
TSPAN7	-6.40	-5.60
TGFB2	-14.50	-5.50
CCL25	-4.87	-5.13
MYC	-4.20	-5.00
AKT3	-4.00	-4.89
CCR6	-15.17	-4.17
CRIPTO 1	-2.30	-4.16
APC2	-11.99	-4.01
AKT1	-2.90	-3.60
TRIB2	-5.67	-3.33
SOCS1	-11.06	-3.06
TGFB1	-2.90	-2.80
TRIB1	-12.30	-2.80
CCL2	-18.00	-2.80
STAT1	-3.40	-2.80
CCND1	-5.60	-2.80
PCDHA10	5.67	4.33
CLDN1	4.39	4.39
VIM	4.00	4.56

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<b>Gene</b>	<b>CRC*</b>	<b>CR-CSC*</b>
<b>NID1</b>	4.02	4.62
<b>CIITA</b>	13.73	4.73
<b>GBP1</b>	6.57	6.77
<b>TTN</b>	4.38	7.38
<b>PCDHA9</b>	18.26	9.26
<b>CD96</b>	12.35	9.35
<b>CCL3</b>	8.37	13.37
<b>SEMA3A</b>	24.45	16.45
<b>CD53</b>	27.49	17.49
<b>RARB</b>	18.20	34.30
<b>SOCS3</b>	153.20	174.50

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\*Values are expressed as fold change variations with respect to the WT cells. Only genes with a fold change >2 in both cell lines are reported.

§Genes are reported starting from the most downregulated to the most upregulated in CR-CSC.