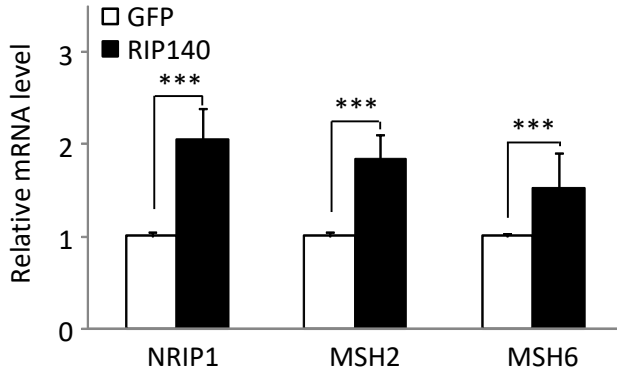
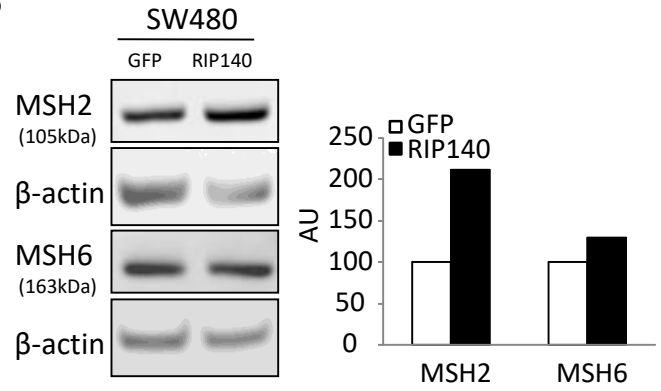
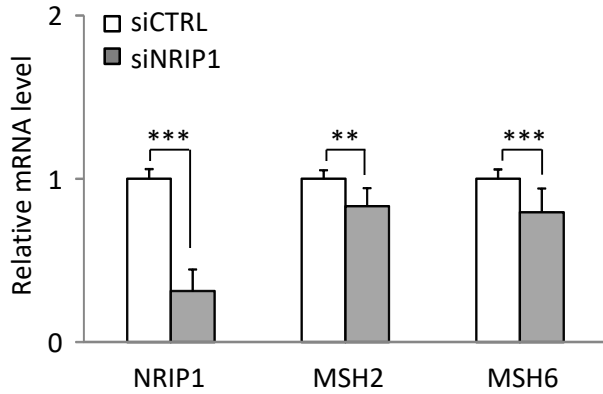
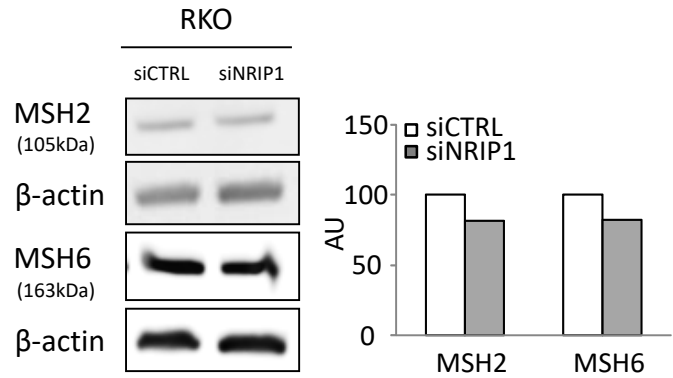


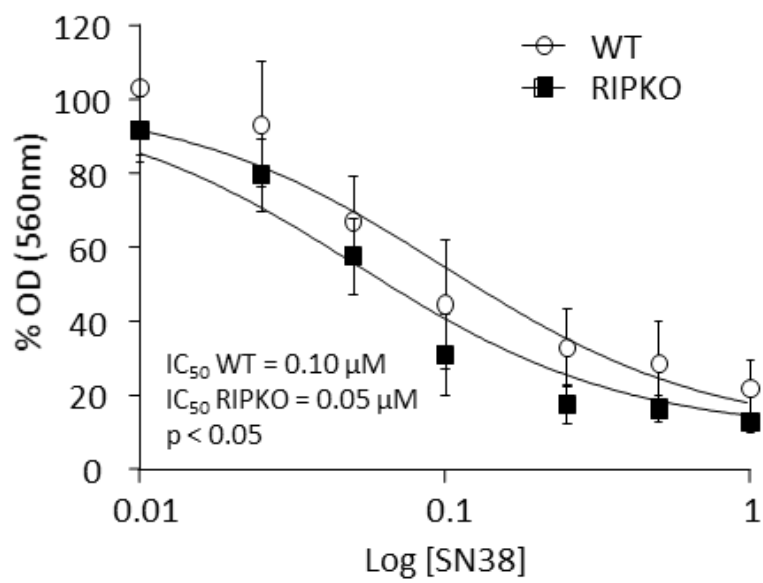
**NRIP1 regulates MSH2/6 expression in transiently transfected HCT116 CRC cells**

**Figure S1**

**A****B****C****D**

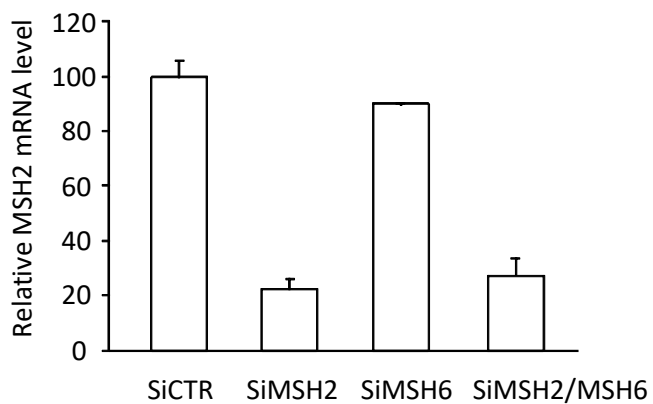
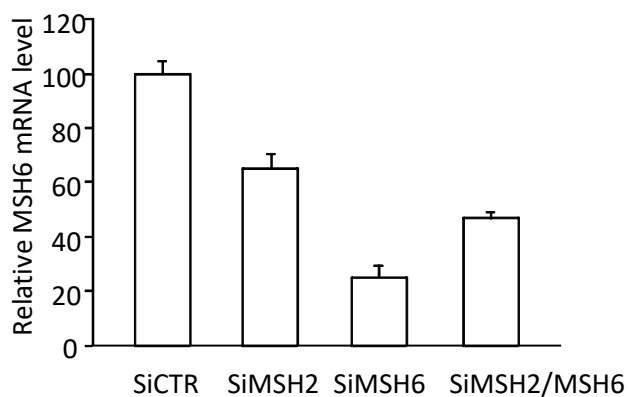
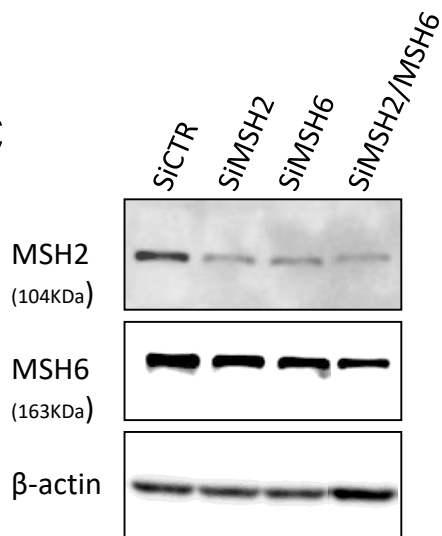
**NRIP1 regulates MSH2/6 expression in other CRC cells**

**Figure S2**

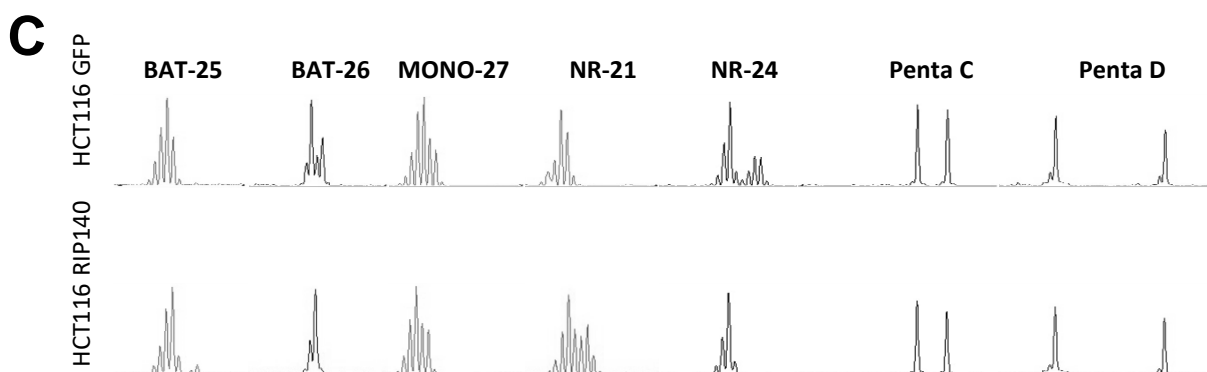
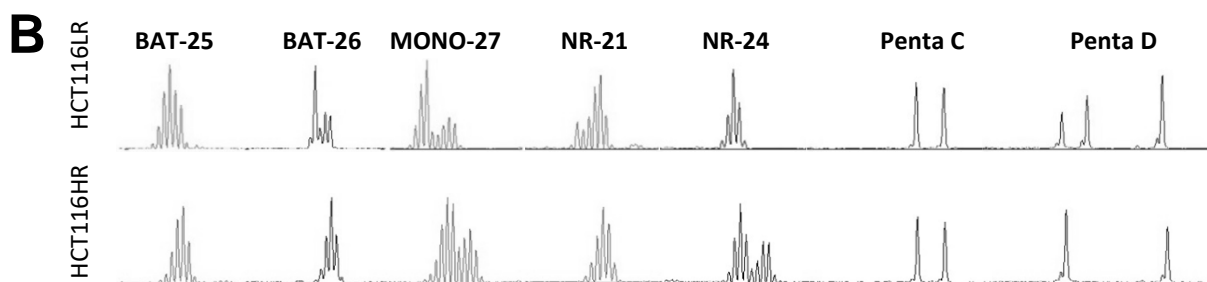
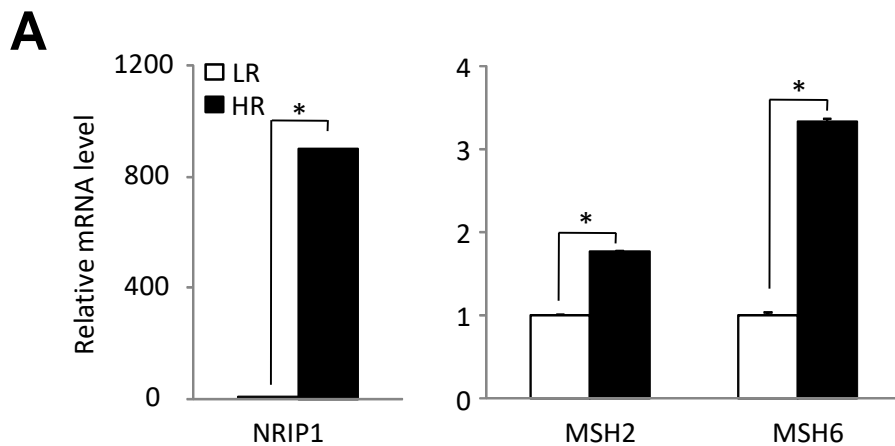


**NRIP1 affects the response to SN38 in MEFs**

**Figure S3**

**A****B****C**

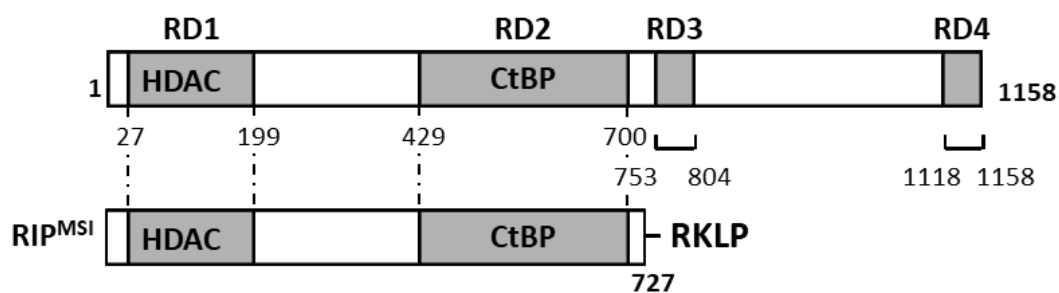
**Validation of MSH2/MSH6 gene knock-down**



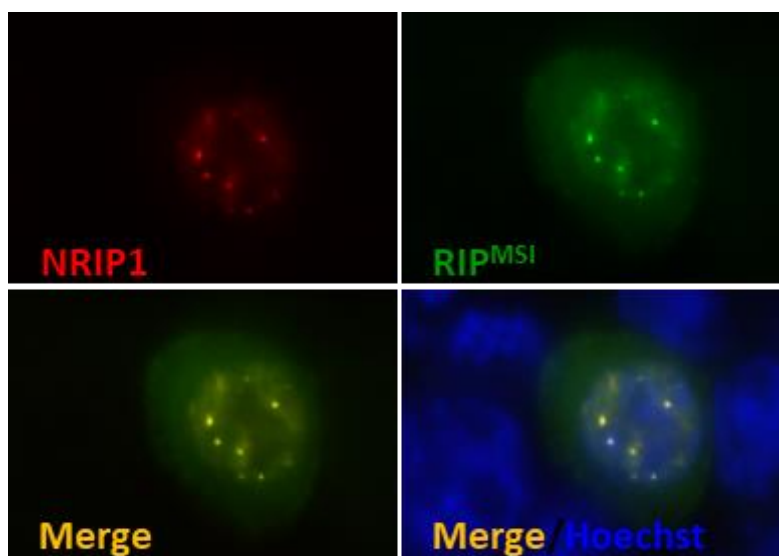
**MSH2 and MSH6 gene expression in the HCT116 cells  
used to monitor MSI**

**Figure S5**

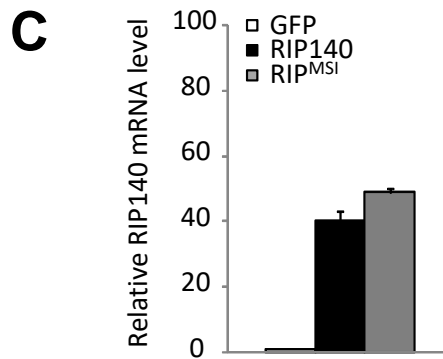
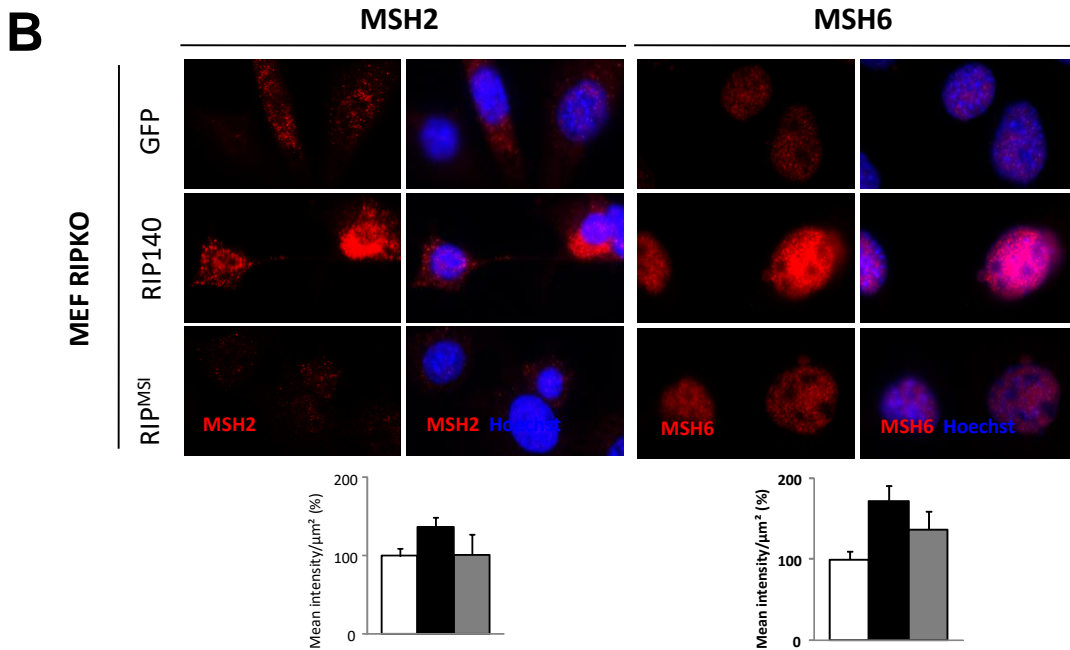
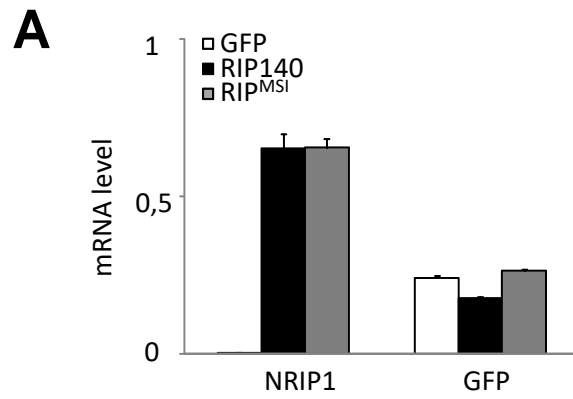
**A**



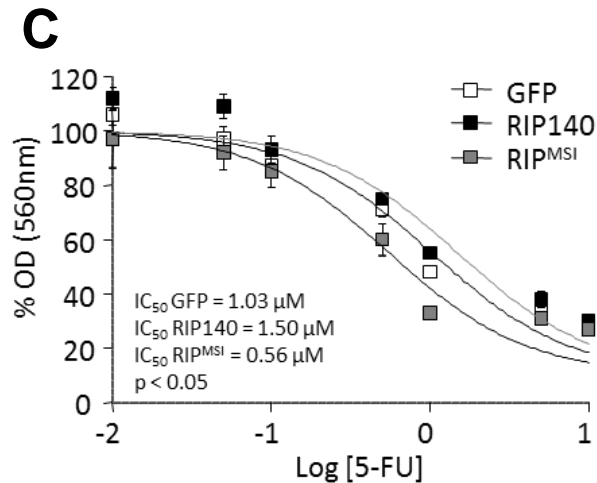
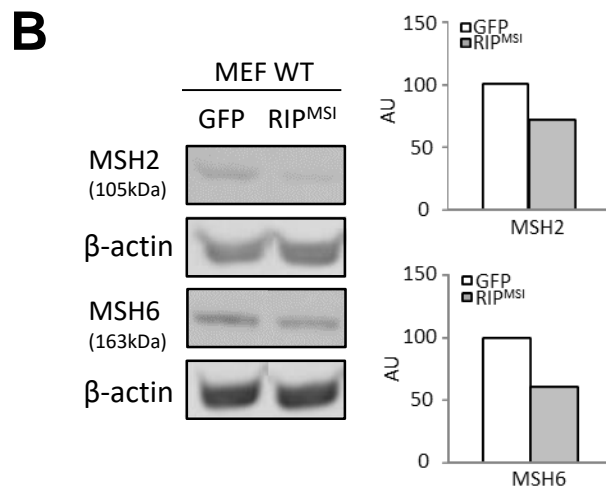
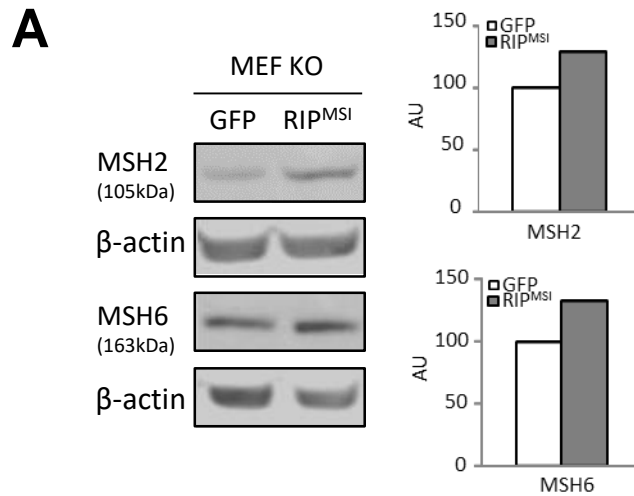
**B**



Subcellular localization of the RIP<sup>MSI</sup> mutation



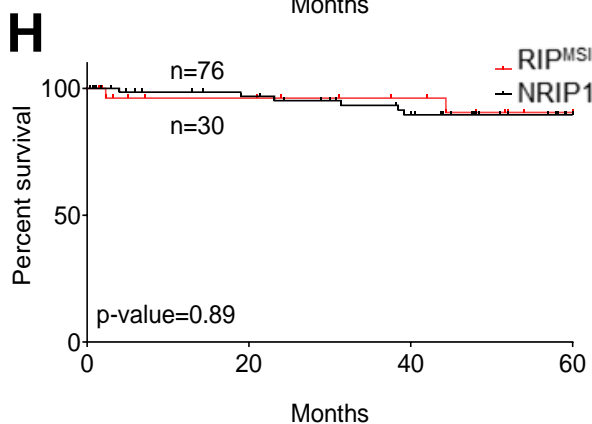
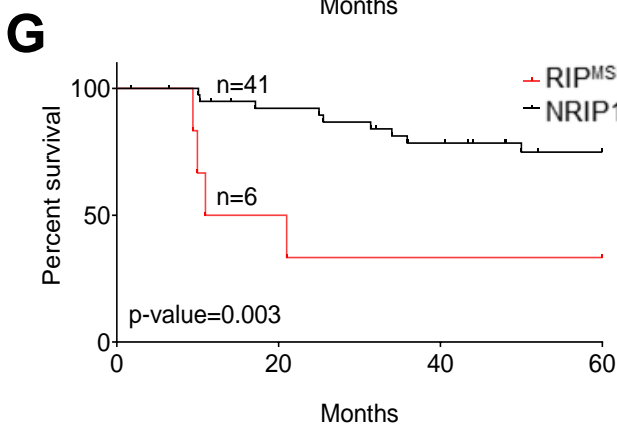
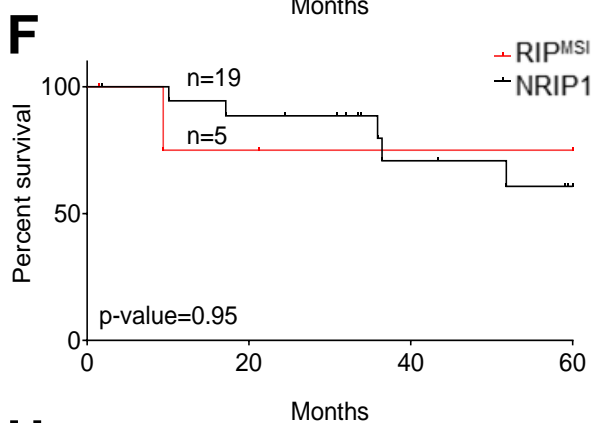
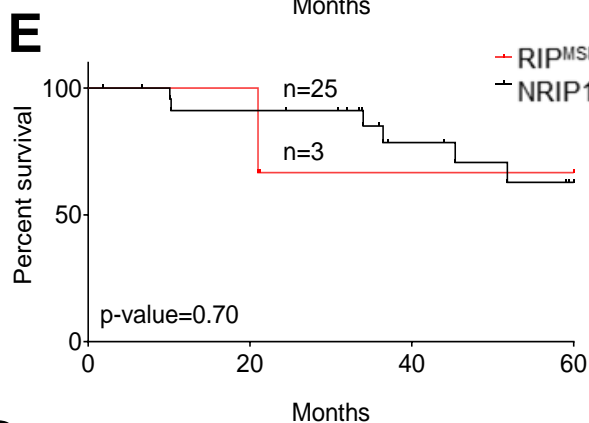
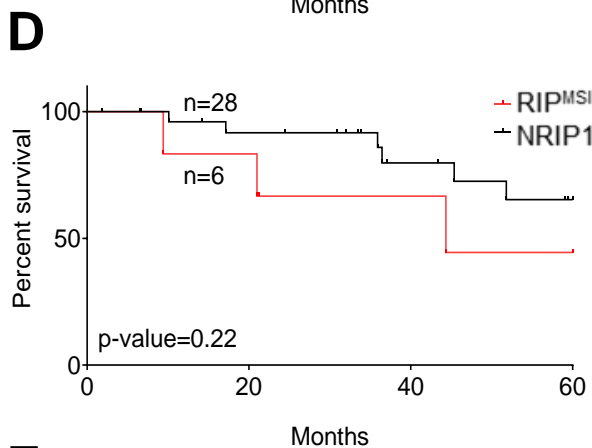
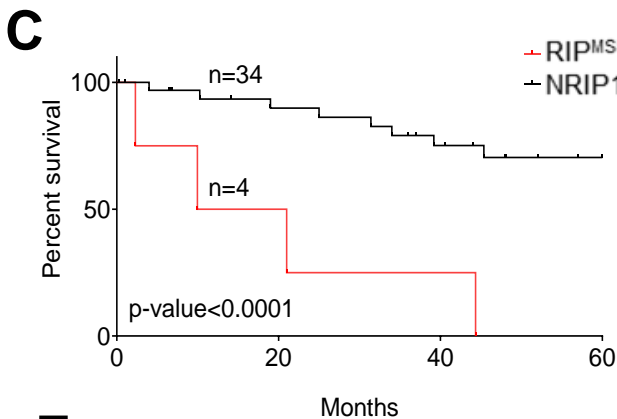
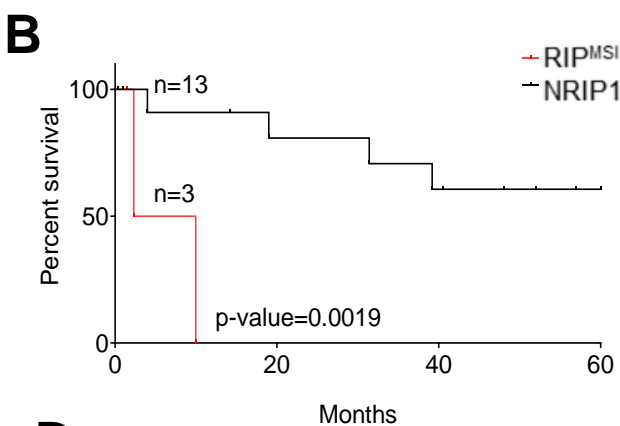
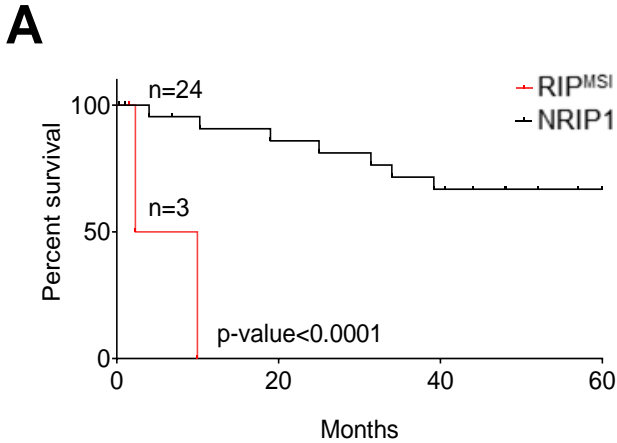
Biological characterization of the RIP<sup>MSI</sup> mutation



**Effect of the RIP<sup>MSI</sup> mutation on MSH2 and MSH6 expression and 5-FU cytotoxic effect**

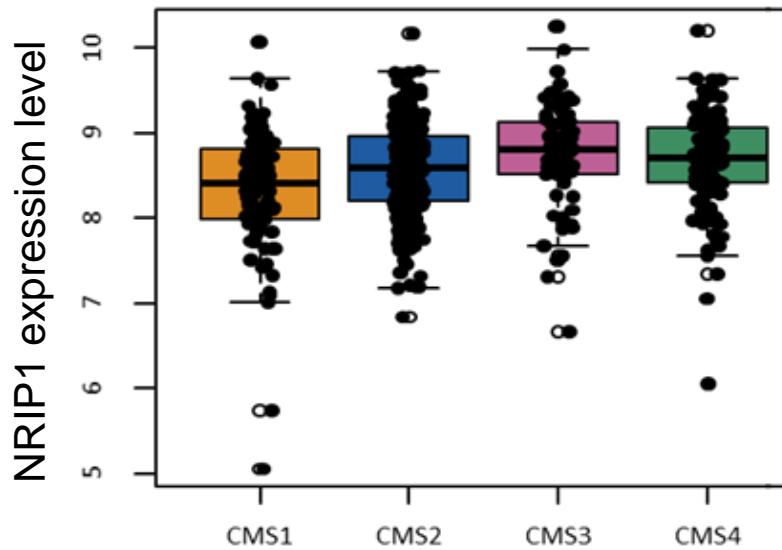
**Figure S8**





**Prognostic value of the RIP<sup>MSI</sup> mutation  
in different subgroups of MSI CRC patients**

**Figure S9**



Subtype	Characteristics	Nb of samples	Tukey's p value vs CMS1
CMS1	MSI immune, BRAF mutations	91	n.a.
CMS2	Canonical WNT activation	232	0.0293
CMS3	Metabolic deregulation	69	0.0001
CMS4	Mesenchymal TGF-b activation	127	0.0002

***NRIP1* expression in the different CRC consensus molecular subtypes**

**Table S1. Primer sequences**

Gene Symbol	Forward Sequence	Reverse Sequence
mLacZ	CCGGTCGCTACCATTACCAG	CCGATTGTCTGTTGTGCC
mNRIP1	AGAACGCACATCAGGTGGCA	GATGGCCAGACACCCCTTTG
mMsh2	TGGCAGTTTTTGTGACTCCT	AAGGAACTCGTGGTTTTCCA
mMsh6	AGGCAAAGGATCTCAACGG	TTAGCCCAAACCAAATCACC
hNRIP1	AATGTGCACTTGAGCCATGATG	TCGGACACTGGTAAGGCAGG
hMSH2	TTCTGACTTCTCCAAGTTTCAGG	GGATCAAATGAAGGTTTTACAAGG
hMSH6	GCGAAGAACCTCAACGGAG	CAGGGGTAAACCCTCCATCTT
MSH2-7	GCATGGGAGTAACATCAGAAGGA	CCGATGTTGGCAGTTTGCTT
MSH6-2	TTTCCGAGGCCTTTCGGGT	CTCCGACCCGGGGTTAGT
MSH6-4	AGCCCCGCGGCGTGAGG	GGCTGGCACACTGGTGGGTA
hRIP <sup>MSI</sup>	GAGTACTTTCATCTCTTAAGGGAGTTT	CCAGTTGCTCCTGGGGAA
siNRIP1	GAAGCGUGCUAACGAUAAA	
siMSH2	UCCAGGCAUGCUUGUGUUGAA	
siMSH6	AUCGCCAUUGUUCGAGAUUUA	

**Table S2. Patients and tumor characteristics (IHC analysis)**

<b>Characteristic</b>	<b>n = 122 n (%)</b>
<b>Age at diagnosis (median, years)</b>	<b>67 [21-89]</b>
<b>Sex</b>	
Male	54 (51)
Female	52 (49)
<b>Tumor site*</b>	
Primary colon cancer	106 (87)
Metastasis	16 (13)
<b>pTNM stage</b>	
I	19 (16)
II	35 (29)
III	35 (29)
IV	14 (14)
<b>MSI/MMR status</b>	
MSS	12 (10)
MSI	12 (10)
MMR mutation	n.d.
No MMR mutation	n.d.
Unknown	98 (80)

\* Multiple sites for 13 patients

**Table S3. Summary of the effects of NRIP1 on the response to cytotoxic drugs in MEFs and HCT116 cells**

Drug	IC <sub>50</sub> ratios (MEFs) WT vs KO	p-value	IC <sub>50</sub> ratios (HCT116) RIP140 vs GFP	p-value
Oxaliplatin [μM]	2.21	< 0.05	3.05	< 0.05
5-FU [μM]	2.03	< 0.01	2.65	< 0.001
SN38 [μM]	1.92	< 0.05	2.06	< 0.05

Table S4. Patient and tumor characteristics

Characteristic	Stage III CRCs n=63		Stage III dMLH1 CRCs n=41		Other CRCs n=153	
	Population n (%)	RIP <sup>MSI</sup> n (%)	Population n (%)	RIP <sup>MSI</sup> n (%)	Population n (%)	RIP <sup>MSI</sup> n (%)
<b>NRIP1</b>						
Wild-type	54 (85.7)	/	36 (87.8)	/	115 (75.2)	/
Mutated	9 (14.3)	/	5 (12.2)	/	38 (24.8)	/
<b>Age</b>						
Age at diagnosis (median, years)	63 [21.8-97]		71 [29.3-97]		71.5 [20.7-93.9]	
<55	24 (38.1)	5 (20.8)	7 (17.1)	2 (28.6)	61 (39.9)	10 (16.4)
≥55	39 (61.9)	4 (10.3)	34 (82.9)	3 (8.8)	89 (58.2)	28 (31.5)*
Missing data	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)
<b>Sex</b>						
Men	35 (55.6)	6 (17.1)	20 (48.8)	3 (15)	74 (48.4)	17 (23)
Women	28 (44.4)	3 (10.7)	21 (51.2)	2 (9.5)	79 (51.6)	21 (26.6)
<b>Tumor site</b>						
Colon	56 (88.9)	7 (12.5)	37 (90.2)	4 (10.8)	134 (87.6)	33 (24.6)
Rectum	7 (11.1)	2 (28.6)	4 (9.8)	1 (25)	17 (11.1)	5 (29.4)
Missing data	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.3)	0 (0)
<b>pTNM stage</b>						
I	/	/	/	/	18 (11.8)	6 (33.3)
II	/	/	/	/	113 (73.9)	28 (24.8)
III	63 (100)	9 (14.3)	41 (100)	5 (12.2)	22 (14.4)	4 (18.2)
<b>BRAF V600E</b>						
No	29 (46)	3 (10.3)	14 (34.1)	2 (14.3)	77 (50.3)	15 (19.5)
Yes	16 (25.4)	3 (18.8)	16 (39)	3 (18.8)	31 (20.3)	11 (35.5)
Missing data	18 (28.6)	3 (16.7)	11 (26.8)	0 (0)	45 (29.4)	12 (26.7)
<b>MLH1 status</b>						
dMLH1	41 (65.1)	5 (12.2)	/	/	/	/
pMLH1	20 (31.7)	4 (20)	/	/	/	/
Missing data	2 (3.2)	0 (0)	/	/	/	/

\*p-value = 0.01 in ≥55-year-old patients with stage III dMLH1 CRC versus other patients with CRC