

Guide RNA sequences (5'-3'):

Name of guide RNA	Target gene/exon	Sequence
<i>CASPASE-8</i> #1	<i>CASPASE-8</i> exon 2	GCCTGGACTACATTCCGCAA
<i>CASPASE-8</i> #2	<i>CASPASE-8</i> exon 7	CGGGGATACTGTCTGATCAT
<i>RIPK1</i> #1	<i>RIPK1</i> exon 2	AGTGCAGAACTGGACAGCGG
<i>RIPK3</i> #1	<i>RIPK3</i> exon 3	GAATTCGTGCTGCGCCTAGA
<i>MLKL</i> #1	<i>MLKL</i> exon 2	CAAGAAACAGTGCCGGCGCC
<i>MLKL</i> #2	<i>MLKL</i> exon 2	GGAGCTCTCGCTGTTACTTC
<i>CASPASE-10</i> #1	<i>CASPASE-10</i> exon 4	AAATGCCAGGAAACTTAGGG

Primer sequences (5'-3') used for Illumina MiSeq sequencing:

Name of guide RNA	Fwd primer sequence	Rev primer sequence
<i>CASPASE-8</i> #1	GGACTTCAGCAGAAATCTT TATG	TAGGCAGAAATTTGAGCCCT GC
<i>CASPASE-8</i> #2	GAGTCAGCTCCTGGGTTG G	ACATGGCCCTTTTGGTATAG C
<i>RIPK1</i> #1	ACAGGGTACAGCTCTGCC GG	GCAGCAGCCAACGGCTCCAC
<i>RIPK3</i> #1	CGGTGCGACTCCAGCTCT C	GTCCCGGTGCAGGAGCAC
<i>MLKL</i> #1	CATTTAAGTCACAGACCGC TTTG	CCCATTAGCCTCCTCCAGGG
<i>MLKL</i> #2	GCAATAGATCCAATATCTG CAGG	TCATCATTGCTGCTCCTTTGG
<i>CASPASE-10</i> #1	GCTGTTATATCTTATTTATC AGTGC	GCCAATTGGTTTAAGAATTC CATG

CRISPR/Cas9 HT29 cell clone number used in this study:

CASP8^{-/-} HT29 clones: 5

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TACCAAATGAAAAGCAAACCTCGGGCATACTGTCTGATCATCAACAATCAC
TACCAAATGAAAAGCAAACCTCGGG-ATACTGTCTGATCATCAACAATCAC
TACCAAATGAAAAGCAAACCTCGG--ATACTGTCTGATCATCAACAATCAC
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RIPK1^{-/-} HT29 clones: 3

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AGTGACTTCCTGGAGAGTGCAGAACTGGACACCGGAGGCTTTGGGAAGG
AGTGACTTCCTGGAGAGTGCAGAACTGGACA-CGGAGGCTTGGGAAGG
AGTGACTTCCTGGAGAGTGCAGAACTGGACA-----TT-----CAAGG
AGTGACTTCCTGGAGAGTGCAGAACTGGACA-C-----
AGTGACTTCCTGGAGAGTGCAGAAC-----CGGAGGCTTGGGAAGG
```

RIPK3^{-/-} HT29 clones: 2

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GCCATGGCAAGTCTGGATAACGAATTCGTGCTGCGCCTAGAAGGGGTTATCGAGAAG
GCCATGGCAAGTCTGGATAA-----GAAGGGGTTATCGAGAAG
GCCATGGCAAGTCTGGATAA-----GAAGGGGTTATCGAGAAG
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MLKL^{-/-} HT29 clones: 1 full knockout, 1 with one wt allele

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TGTCTGGAAGGAGCTCTCGCTGTTACTT-CAGGTTGAGC
TGTCTGGAAGGAGCTCTCGCTGTTA-TT-CAGGTTGAGC
TGTCTGGAAGGAGCTCTCGCTGTTACTT-CAGGTTGAGC
```

CASP10^{-/-} HT29 clones: 11

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GATTCTCTTGTAGACCTCCCT-AAGTTTCCTGGCATTCTAGAC
GATTCTCTTGTAGACCTCC-----TGGCATTCTAGAC
GATTCTCTTGTAGACCT-----GGCATTCTAGAC
GATTCTCTTGT-----TTCTGGCATTCTAGAC
GATTCTCTTGTAGACCTCCCTAAGTTTCCTGGCATTCTAGAC
```

RIPK1^{-/-} *CASP8*^{-/-} HT29 clones: 7

RIPK3^{-/-} *CASP8*^{-/-} HT29 clones: 12

MLKL^{-/-} *CASP8*^{-/-} HT29 clones: 13

RIPK3^{-/-} *CASP10*^{-/-} HT29 clones: 10

MLKL^{-/-} *CASP10*^{-/-} HT29 clones: 5

RIPK3^{-/-} *CASP8*^{-/-} *CASP10*^{-/-} HT29 clones: 5

MLKL^{-/-} *CASP8*^{-/-} *CASP10*^{-/-} HT29 clones: 8

Supplementary figure 5