Figure S1

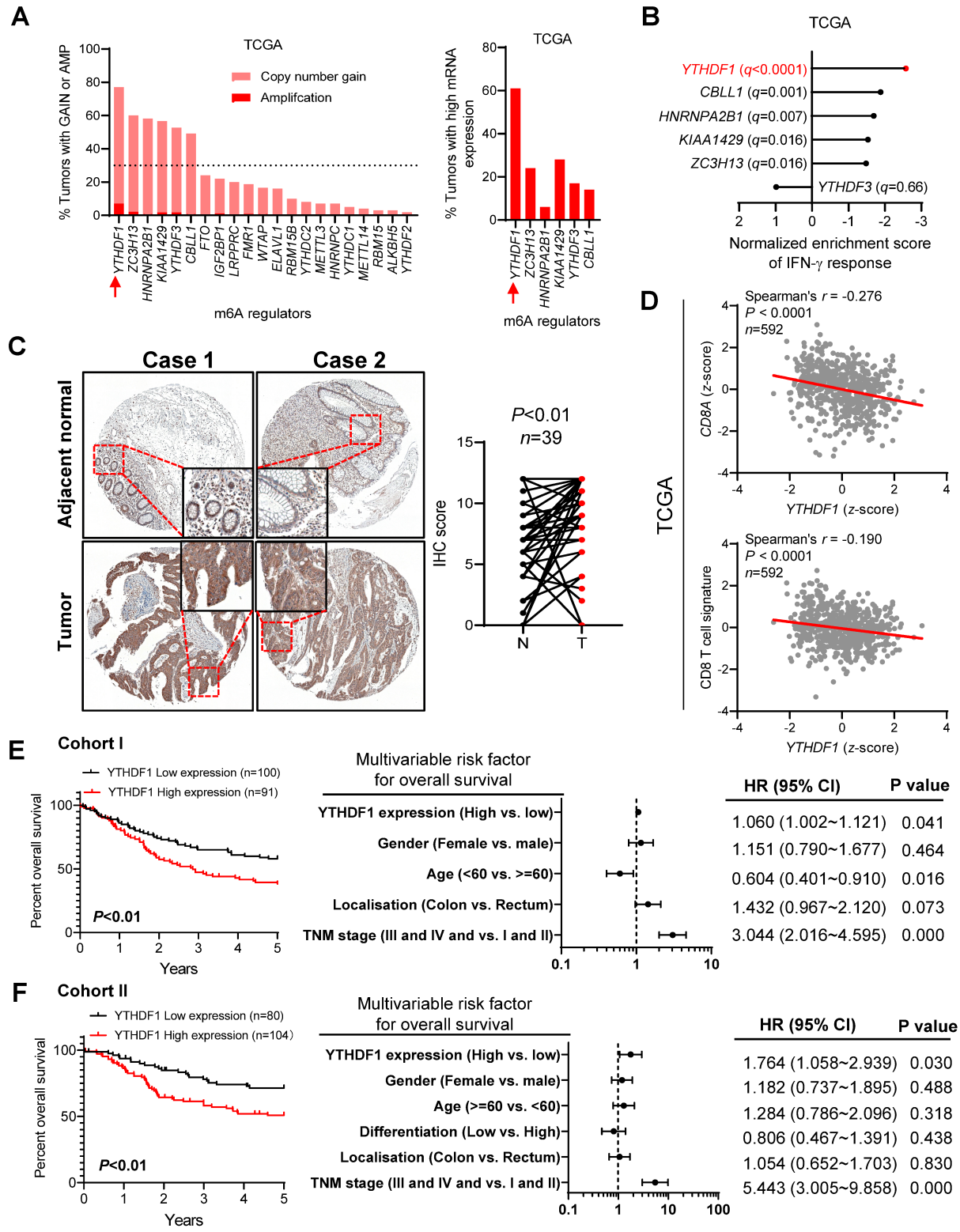

Figure S1. (**A**) Left: Percentage of tumors (*n*=526) that display copy number gain (GAIN) or amplification (AMP) of the indicated m6A regulators. Right: Percentage of tumors that display high mRNA expression of the indicated m6A regulators. High mRNA expression was defined as equal to or greater than two s.d. above the mean of diploid samples. (**B**) Gene set enrichment analysis (GSEA; *n*=524) for signature of IFN-γ response with the indicated m6A regulators. FDR lower than 0.0001 was highlighted in red. (**C**) Representative images and quantification of IHC comparing YTHDF1 expression between adjacent normal tissue and tumor tissue in cohort II. (**D**) Correlation of *YTHDF1* expression and *CD8A* expression or CD8 T cell signature in colorectal cancer. Data in **A**, **B**, and **D** were from TCGA. (**E**) In cohort I, patients with high expression of YTHDF1 (*n*=91) have a poor prognosis than those with low expression (*n*=100) based on the log-rank test. Multivariate Cox regression analyses illustrated that YTHDF1 was an independent prognostic factor in CRC (*P*<0.01). (**F**) In cohort II, patients with YTHDF1 high expression (*n*=104) had a poor prognosis than patients with low expression (*n*=80) according to the log-rank test (*P*<0.01). Multivariate Cox regression analyses revealed that YTHDF1 was an independent prognostic factor in CRC.

Figure S2

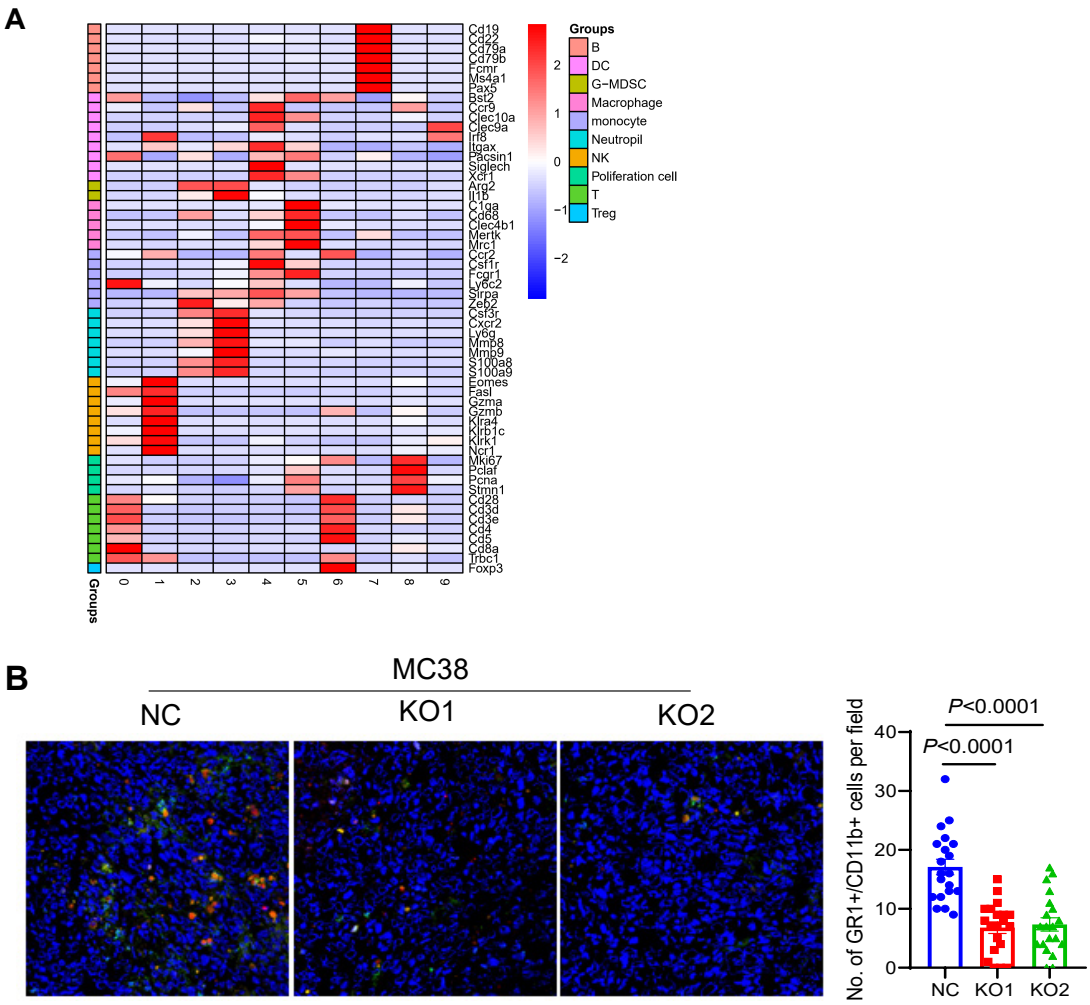

Figure S2. (**A**) Heatmap displaying the scaled expression patterns of top marker genes within CD45^{+} cells from wildtype mice. Red: high expression; Blue: low expression. (**B**) Immunofluorescence identifying MDSCs in subcutaneous tumors from C57BL/6 injected with the indicated MC38 cells. Red: CD11b. Green: Gr1. Blue: DAPI. [Two tailed t-test (B)].

Figure S3

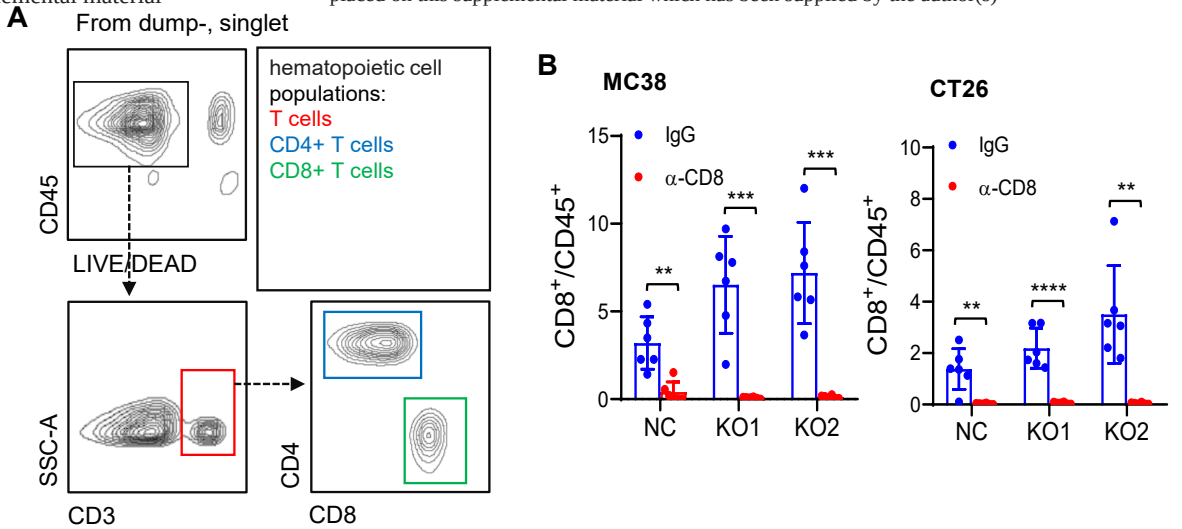

Figure S3. (**A**) Gating strategies to identify $CD4^+$ or $CD8^+$ T cells in the blood collected from mice. (**B**) Flow cytometry analysis on $CD8^+$ T cells in blood from mice injected subcutaneously with MC38 or CT26. $CD8^+$ T cells depletion was performed with anti-mouse CD8 antibody (α-CD8) at 200 μg/mouse once every three days. [Two tailed t-test (B)].

Figure S4

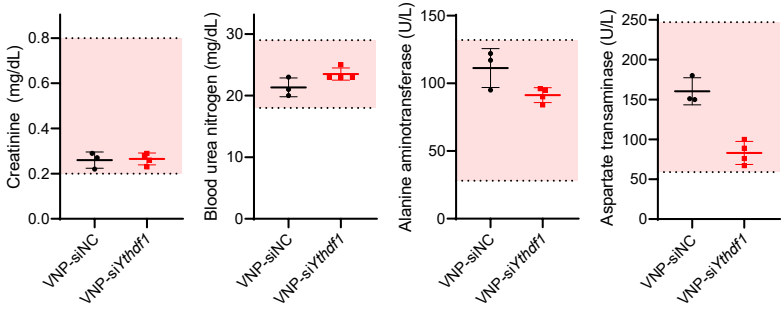

Figure S4. Serum markers from CD34$^+$ humanized mice bearing HCT116 tumors that were treated with the indicated vesicle-like nanoparticles (VNP). Pink box indicates the reference interval of each indicator.

Figure S5

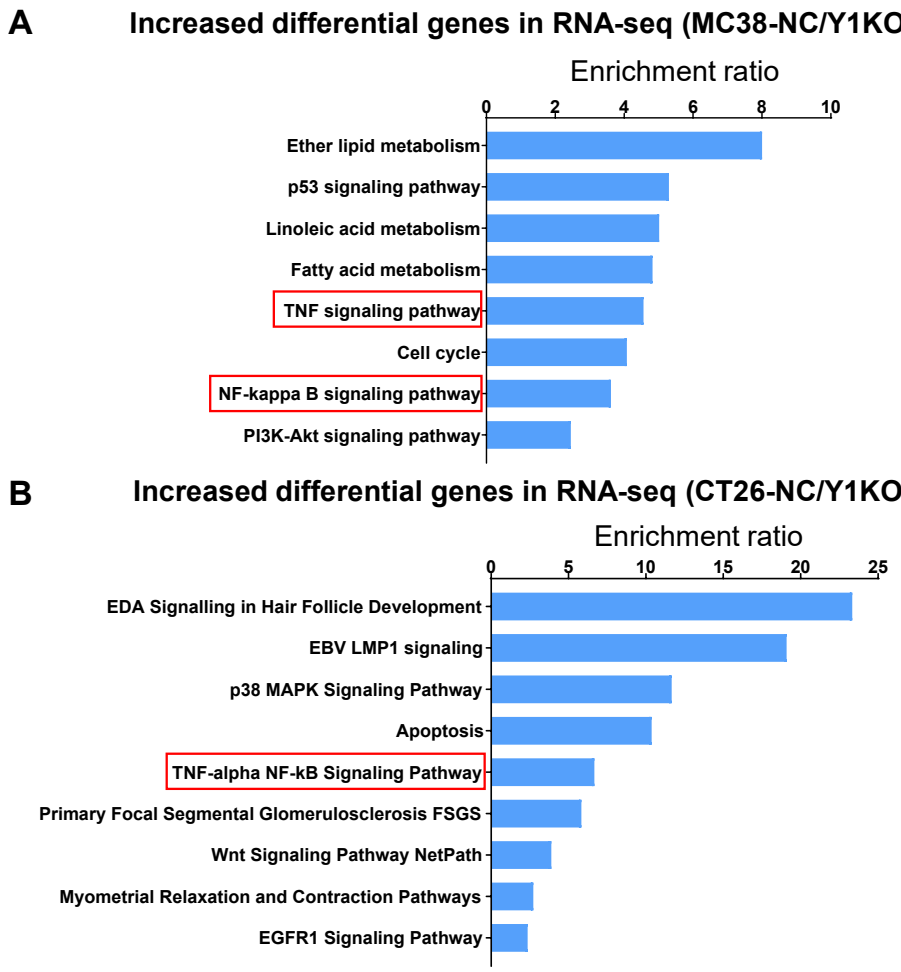

Figure S5. Increased differential genes (NC/Y1KO) were enriched in TNF/NF-κB signaling pathway. (**A**) Pathway analysis (KEGG) for increased differential genes of RNA-seq in MC38-NC compared to MC38-Y1KO. (**B**) Pathway analysis (Wikipathway) for increased differential genes of RNA-seq in CT26-NC compared to MC38-Y1KO. Y1KO: *Ythdf1* knockout.

Figure S6.

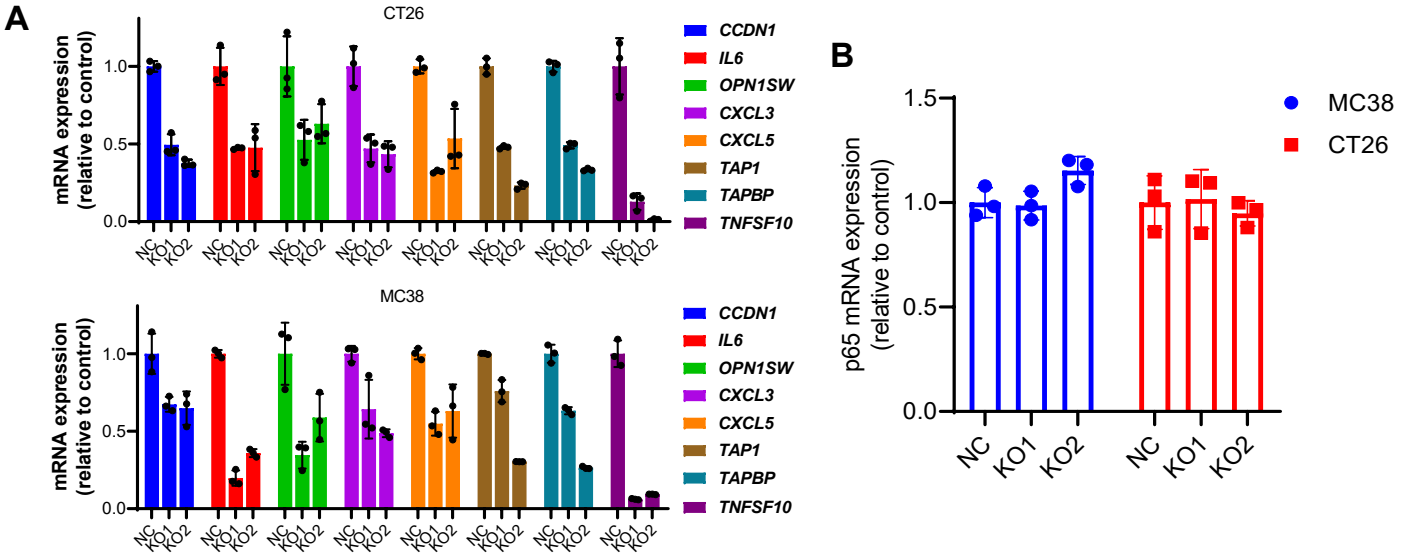

Figure S6. (**A**) RT-qPCR measuring mRNA expression of genes reported to be NF-κB targets in the indicated MC38 or CT26 clones. (**B**) RT-qPCR measuring p65 mRNA level in the indicated MC38 or CT26 clones. Data was acquired from technical triplicates. NC: control; KO: *Ythdf1* KO.

Figure S7.

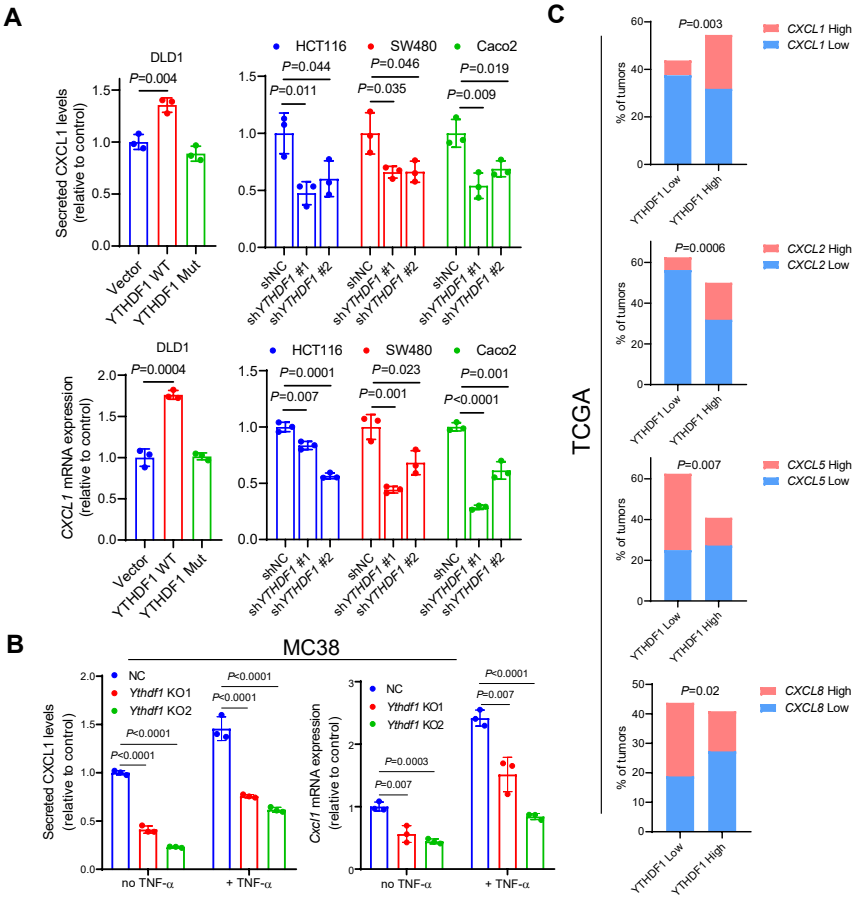

Figure S7. (**A**) RT-qPCR measuring *CXCL1* mRNA levels (top) and ELISA measuring CXCL1 secretion in supernatant (bottom) with the indicated human CRC cells. (**B**) Secreted CXCL1 levels measured by ELISA (left) and *Cxcl1* mRNA expression measured by RT-qPCR (right) in control or *Ythdf1*-depleted MC38 treated with or without TNF-α at 10ng/ml for eight hours. (**C**) Association between the expression of *YTHDF1* and CXCL1 or other CXCL family members in stage IV tumors (*n*=85) from TCGA CRC dataset. YTHDF1 Low: *n*=16; YTHDF1 High: *n*=22. [Two-tailed t tests in (B and C); chi-square tests in (D)]

Figure S8

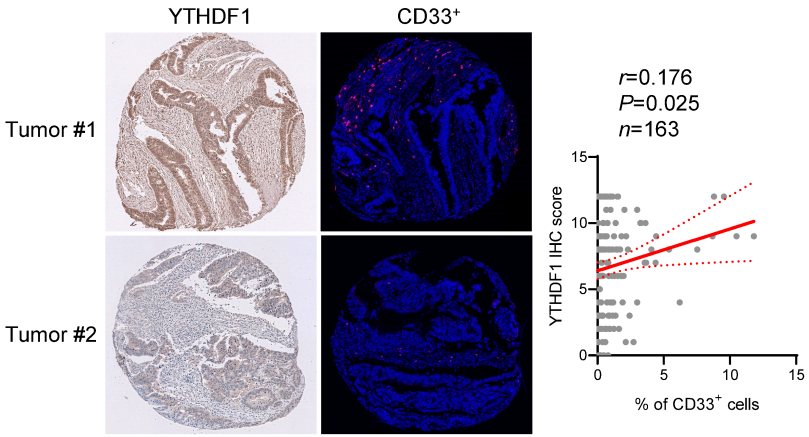

Figure S8. Representative images (left) of IHC of YTHDF1 and immunofluorescence of CD33 on CRC tissue microarray (n=163) from cohort I. Right panel: correlation of YTHDF1 IHC score and percentage of $CD33^+$ cells. All statistics were determined with Pearson correlation test.

Figure S9

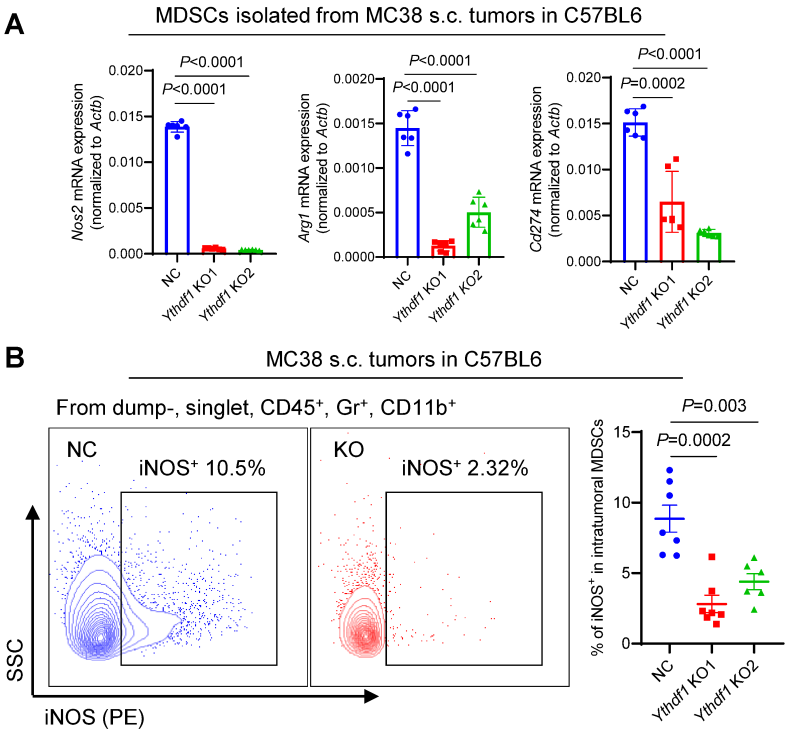

Figure S9. (**A**) mRNA expression of MDSC functional markers (*iNos*, *Arg1*, *Cd274*) in MDSCs isolated from *Ythdf1*-WT and *Ythdf1*-KO MC38 allografts. (**B**) Representative images (left) and quantification (right) of iNOS$^+$ MDSCs in *Ythdf1*-WT or *Ythdf1*-KO MC38 allografts by flow cytometry. [Two tailed t-test (A and B)].