**SUPPLEMENTARY Methods**

**Organoid transduction and transgenesis.** For generation of *ApcKO; p53KO* (AP) tumor organoids, single organoids cells from a *p53fl/fl* mouse (1) were transfected using Lipofectamine® 2000 (Thermo Fisher Scientific) as described previously (2) using Cas9 plasmid (Addgene #41815, kind gift of George Church), gRNA plasmid targeting mouse *Apc* (3) and Cre plasmid (Addgene #30205, a kind gift from Darrell Kotton). Transfected cells were seeded in full medium supplemented with 10 µM Y-27632 and after 3 days, Rspondin-1 was withdrawn (EN medium) and 5 µM Nutlin-3 (Biomol) was added to select for *Apc* and *p53* loss, respectively. AP organoids were clonally expanded, genotyped (see below) and transduced with lentivirus. Lentiviral transduction was performed as described (4). LentiNICD-blast was used alone to obtain APN organoids, or together with either pLV-Pgk::EGFP-IRES-DsRed-P2A-puro, pLV-Pgk::Sfrp1-IRES-DsRed-P2A-puro or pLV-Pgk::Dkk1-IRES-DsRed-P2A-puro. APN-control (control) and APN-Sfrp1 (Sfrp1) or APN-Dkk1 (Dkk1) were maintained in EN medium supplemented with 0.5 µg/ml of Puromycin and 1 µg/ml Blasticidin. *ApcKO; p53KO; Tgfbr2KO; KrasG12D(OE)* (APTK) mouse colon tumor organoids, weredescribed recently (5) and were cultured in medium deprived from Rspondin-1, EGF and Noggin and supplemented with 0.5 µg/ml of Puromycin to maintain transgenic KrasG12D expression. All organoid lines were clonally expanded and genomic DNA was extracted using DNeasy Tissue and Blood kit (Qiagen) according to the manufacturer’s instructions. *Apc* loss-of-function mutations were confirmed by Sanger sequencing as described before (3). *p53* mutation was confirmed by PCR using the following primers: mp53\_flox\_fw: AGTGCCATTGGTCCATGGAT, mp53\_flox\_rev: AGCACATAGGAGGCAGAGAC and mp53\_del\_rev: GCCAGGAACCACTACTCAGA.

**Image processing and analysis.** For measurement of organoid size, APN-Dkk1, APN-Sfrp1 and their controls were seeded at low density, cultured for 3 days and 3 images per well for at least 3 independent wells were taken using an Evos® microscope (Thermo Fisher Scientific; 2X objective). The organoid size was then measured using the Fiji software. Shading correction was performed with the ‘FFT\_Filter’ plugin. The images were then converted to binary and the ‘Analyze Particles’ command was used with the following parameters: size (pixel2) > 100 and circularity: 0.1-1 to measure the area (A) of the organoids. The diameter (D) was calculated using the following formula: D=2√A/ π. For IHC staining (DAB/hematoxylin), at least 6 images of randomly chosen regions per tumor were exported from ScanScope®CS2 using the Aperio® eSlide manager software (Leica). Using the Fiji software, signals were quantified as follows: RGB images were color deconvoluted using the command ‘H&E DAB’ followed by auto-thresholding. Images were converted into binary format, and regions of interest (ROIs) were quantified using the ‘Measure’ tool. The ‘Image calculator’ tool in addition to ‘AND’ function were used to measure double-positive regions. The relative areas were calculated by dividing the ROI of the marker per total positive area. For immunofluorescence stainings, the images were first converted to RGB, channels were split using the ‘Split Channels’ tool, followed by auto-thresholding and then processed as above. For Zeb1 the Zeb1/DAPI double positive signal was determined. Tumor invasion was evaluated as reported previously (6) from stained sections. Briefly, β-catenin-positive cell clusters of less than 10 cells were counted in at least 10 visual fields at the invasive front per tumor.

**RNA sequencing analyses.** 2 µg RNA was used for library synthesis using TruSeq® Stranded Total RNA Library Prep (Illumina). For sorted tumor cells 2 µg RNA from 3 independent control tumors and 3 pools of Sfrp1 tumors (from 3 mice each) was used. For sorted CAFs, 25 ng RNA from 3 independent control tumors each or from 3 pools of Sfrp1 tumors (from 2 mice each) was used for library synthesis using SMART-Seq® v4 Ultra® Low Input RNA Kit (Takara Bio). RNA Sequencing was performed using the HiSeq SBS V4 50 cycle kit (Illumina) and run on a HiSeq 2000 instrument (Illumina). Sequencing data was processed and analyzed as described previously (7). Annotation and conversion to mouse/human gene symbols was performed using biomaRt (version 2.28.0). Differentially expressed genes from all comparisons and experiments are shown in Tables S2-5.

Gene Set enrichment Analysis (GSEA) was carried out as described previously (7) using the ‘GSEA preranked’ tool from the GSEA software (version 2.2.3; Broad Institute) and compared against the MSigDB data base version 6.2 (Broad Institute). Normalized enrichment scores (NES) with q-values < 0.01 were considered statistically significant (Table S6). iCAF and myCAF signatures (Table S7) were derived from data in (8) by filtering the top 200 genes with adjusted *p*-value < 0.01.

The ‘Xenome’ tool was used to deconvolute human and mouse transcripts from xenograft bulk RNA sequencing data (9). In short, an index file was constructed from the human (graft) and mouse (host) reference genomes using hg38 (for human) and mm10 (for mouse) FASTA files from NCBI. The ‘classify’ function was then used to sort the reads for ‘graft’ and ‘host’ as new FASTQ files. Differential analysis for host reads was performed using the ‘limma’ tool (version: 3.9) (10) then subjected to the pipeline for RNA sequencing data described above and differential gene expression is shown in Table S8.

**NicheNet analysis**. Analysis was performed using the ‘nichenetr’ R package as described recently (11). The *in vivo* RNAseq data of sorted Sfrp1 tumor (Table S3) and Pdgfrα+ cells (Table S4) was used as input to investigate interactions between sender cells (iCAFs) and receiver cells (tumor) that showed an EMT phenotype. Gene expression was filtered for baseMean > 20 and log2 fold ratio > 0.25 in both conditions. The signature ‘HALLMARK\_EPITHELIAL\_MESENCHYMAL\_TRANSITION’ was downloaded from MSigDB (version 7.1, Broad Institute) and applied as phenotype signature in NicheNet to determine target genes, ligand-target and ligand-receptor interactions involved in EMT. The ‘predict\_ligand\_activities’ function was used and the top ranked ligands were plotted according to their Pearson correlation coefficient. For ligand-target analysis, a heatmap was generated from the ’Regulatory potential’ scores of interactions between the top-ranked ligands and the 100 most strongly expressed EMT-related genes using the ‘predict\_ligand\_activities’ function. All potential interaction scores below the 0.25 quantile were set to zero and heatmap visualization was performed using the ‘make\_heatmap\_ggplot’ function of the dplyr package. For the ligand-receptor interactions, only curated data (‘bona fide’ interactions) was considered, before heatmap visualization as above.

**Patient data *in silico* analysis**. The microarray expression data of GSE39582 dataset n = 585 (12) was obtained from the NCBI-GEO repository using the GEOquery R package. The expression values were summarized, log2 transformed and Z-scores were then calculated using Scale() function in R. The probes were annotated using the biomaRt R package. For genes with multiple probes, the probe with highest intensity was chosen as representative of that gene. CMS classification was obtained from reported data (13). The ‘Wnt score’ was calculated for each patient by summing the Z-scores of the reported Wnt target genes: *AXIN2, ASCL2, LGR5, BMP4, ZNRF3, MRTO4, HILPDA, KITLG, NOP16, PPIF, SOX4, PAAF1*, and *ZIC2* (14). The ‘Wnt antagonist score’ was calculated by summing the Z-scores of *DKK1, DKK2, DKK3, DKK4, SFRP1, SFRP2, SFRP4* and *SFRP5*. Kaplan-Meier plots were generated using GraphPad Prism software and the hazard ratio (HR) and statistical analyses were performed using the log-rank test. Data were not adjusted for covariates.

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