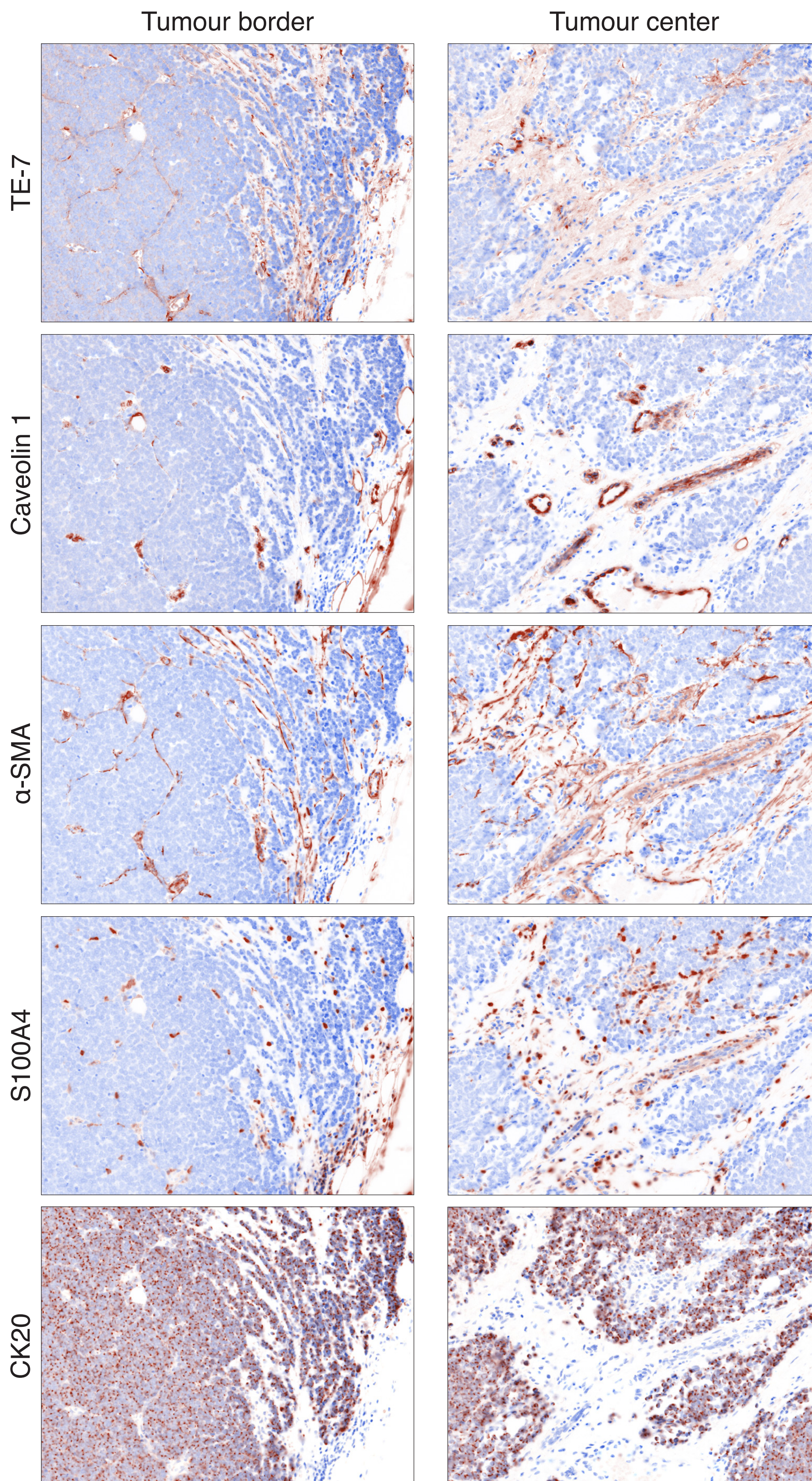
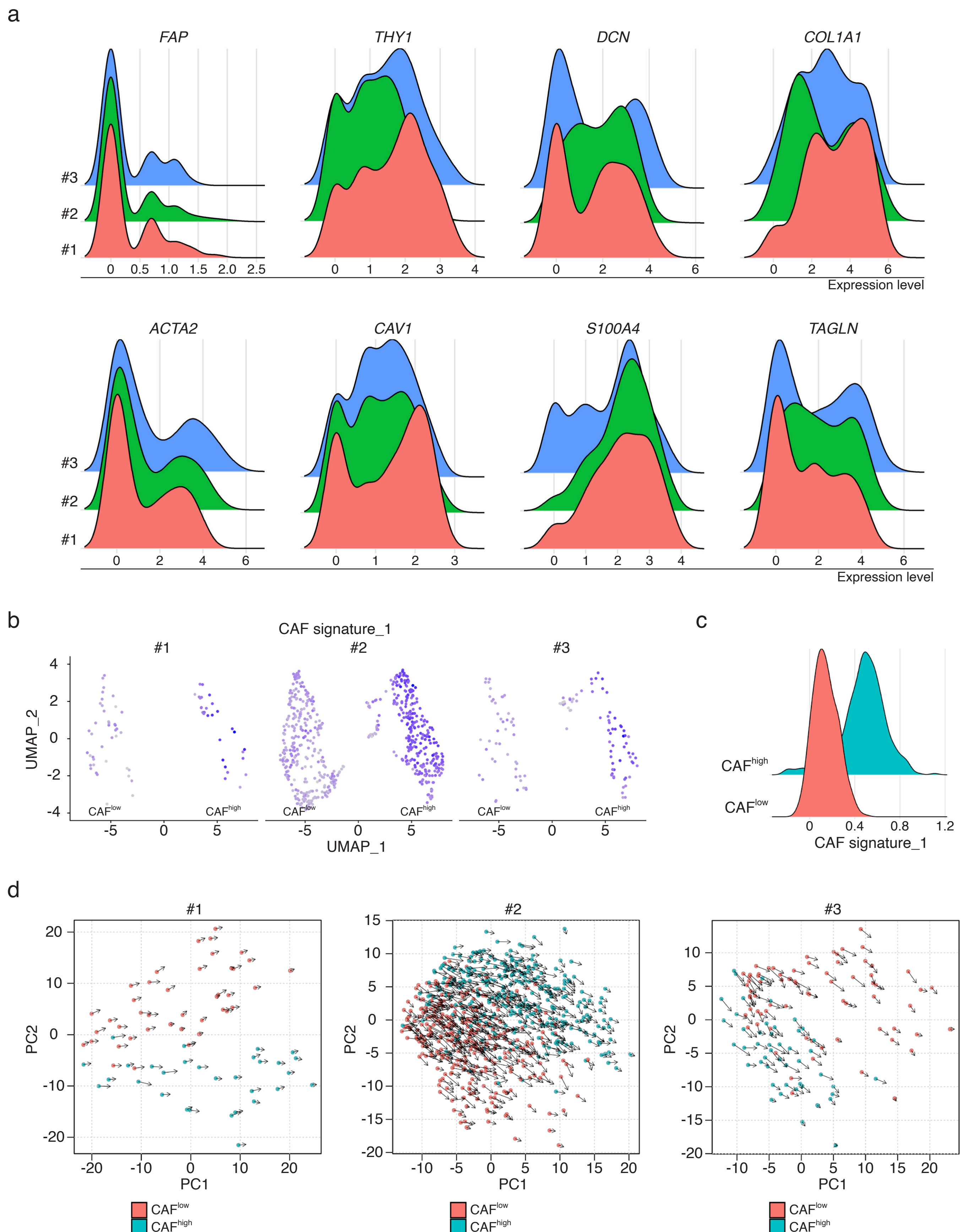
Suppl. Figure S1



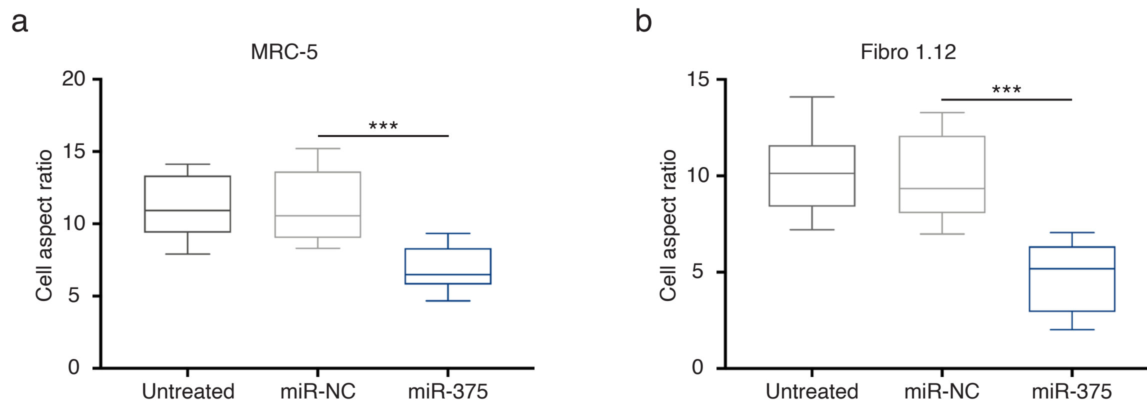
Suppl. Fig. S1: Expression of fibroblast activation markers in MCC via Pathology Views
Pathology Views™ was applied to generate six single marker pseudo-bright field images of the images shown in Fig. 1a in which the individual signals for TE-7, Caveolin-1, α-SMA, S100A4 and CK20 were converted into 3, 3 diamin-obenzidine (DAB)-like color. of the estimated future cell state of each cell.

Suppl. Figure S2



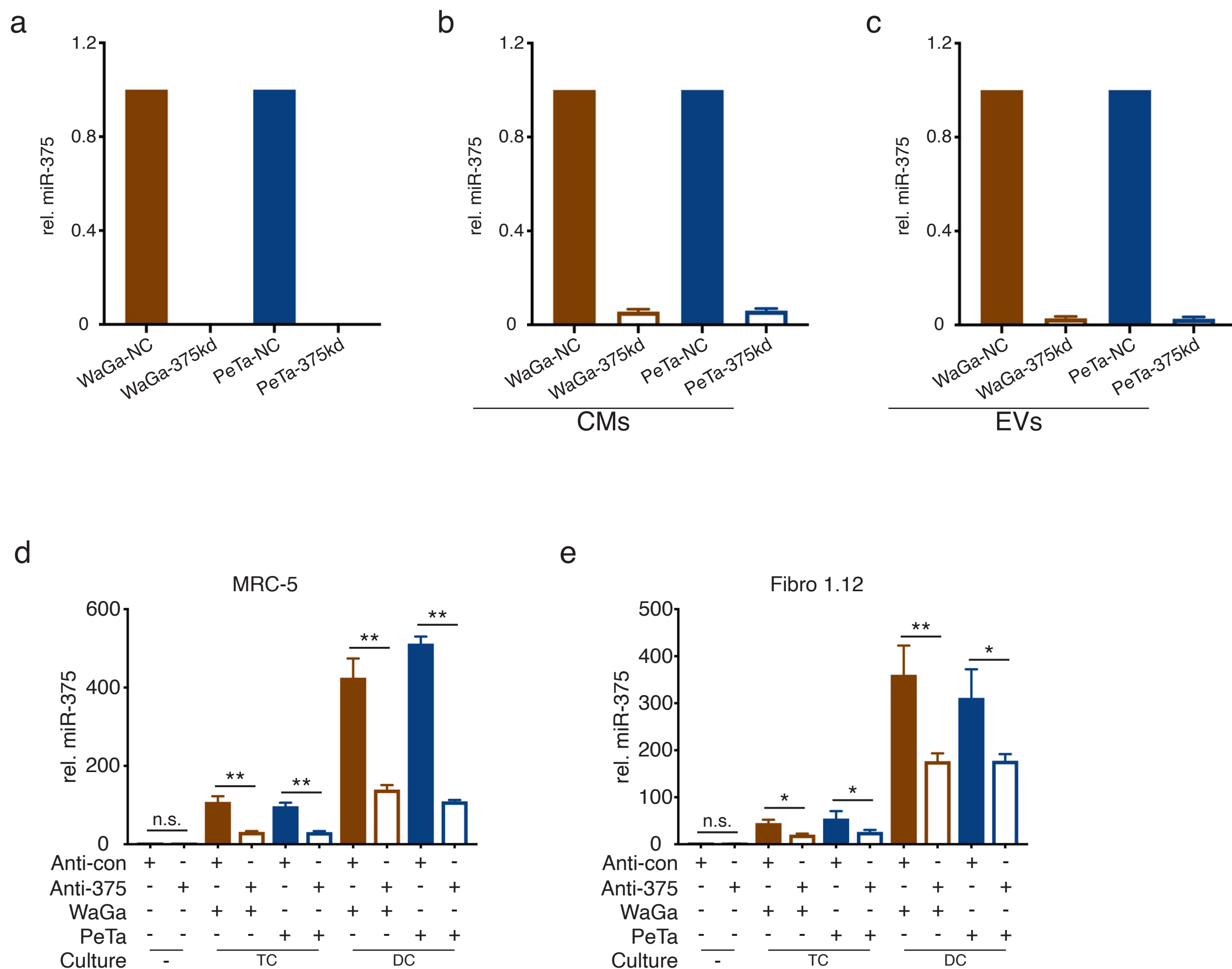
Suppl. Fig. S2: Heterogeneity of the mRNA expression of fibroblast polarization-related genes in three MCC tumors a: mRNA expression levels of selected CAF markers in identified fibroblasts in three MCC tumors. b: UMAP plot of the CAF signature scores of fibroblasts in three tumors. These fibroblast clusters were annotated as CAFhigh and CA-Flow. c: CAF signature scores were generated for merged fibroblast clusters from three tumors based on the mRNA expression of 88 CAF marker genes. d: PCA plot of the RNA velocity with the speed vectors of the two fibroblast clusters in three tumors. The arrows indicate the location of the estimated future cell state of each cell.

Suppl. Figure S3



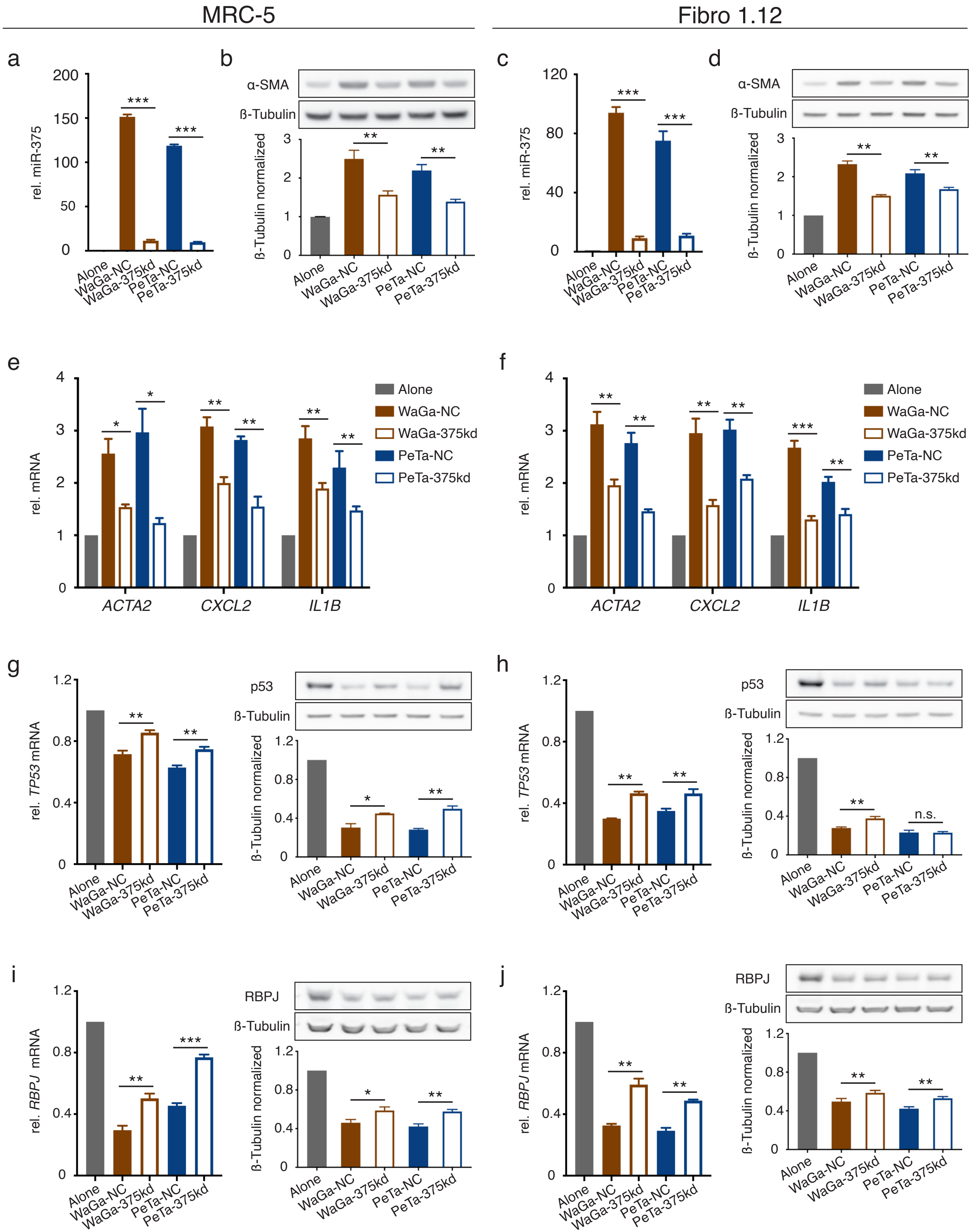
Suppl. Fig. S3: Overexpression of miR-375 in MRC-5 and primary skin fibroblasts induces a CAF-like morphology change
a- b: The graphs show the values of cell aspect ratio (length/ width) of MRC-5 (a) and Fibro1.12 (b) under indicated conditions (n= 50), presented as box-and-whisker plots. *** indicates $p<0.001$.

Suppl. Figure S4



Suppl. Fig. S4: miR-375 antagomirs transfected into MCC cells or fibroblasts result in miR-375 knockdown
a- c: miR-375 antagomirs were transfected into WaGa and PeTa cells via nucleofection. Total RNAs from MCC cells, conditioned mediums (CMs) and isolated Extracellular vesicles (EVs) were used for miR-375 expression determination. The relative miR-375 expression level in MCC cells (a), CMs (b) and EVs (c) under the indicated conditions was determined by RT-qPCR. d, e: miR-375 antagomirs were transfected into MRC-5 and Fibro 1.12 cells using lipofectamine. The relative miR-375 expression level in fibroblasts under the indicated coculture conditions was determined by RT-qPCR. Cq values were normalized to U6 expression (a, d, e) or spiked cel-miR-39 (b, c) and compared to the ΔCq of the corresponding control. Experiments were biologically replicated trice and were performed in triplicates. The error bars indicate the SDs; * indicates $p<0.05$, ** indicates $p<0.01$.

Suppl. Figure S5



Suppl. Fig. S5: miR-375 antagomirs in MCC cells diminish co-culture induced fibroblast polarization
MRC-5 cells (a, b, e, g, i) or Fibro 1.12 primary skin fibroblasts (c, d, f, h, j) were co-cultured with WaGa or PeTa cells transfected with miR-375 antagomirs in Transwell system for 72 hours. a, c: The relative miR-375 expression level in fibroblasts under the indicated conditions was determined by RT-qPCR. b, d: α-SMA protein expression in fibroblasts under the indicated conditions was determined by immunoblotting; β-tubulin served as loading control. e, f: The relative ACTA2, CXCL2 and IL1B expression level in fibroblasts under the indicated conditions was determined by RT-qPCR. g, h: Relative expression of TP53 mRNA (left) and protein (right) level in fibroblasts under the indicated conditions was determined by RT-qPCR and immunoblotting. i, j: Relative expression of RBPJ mRNA (left) and protein (right) level in fibroblasts under the indicated conditions was determined by RT-qPCR and immunoblotting. For all RT-qPCR experiments, Cq values were normalized to HPRT mRNA or U6 expression and compared to the ΔCq of the corresponding untreated MRC-5 or Fibro.1.12 cells. Experiments were biologically replicated trice and were performed in triplicates. The error bars indicate the SDs; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicate $p< 0.001$.