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 diaminobenzidine (DAB)-like color. of the estimated future cell state of each cell.
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 CAFlow. 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. 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 Fibro 1.12 (b) under indicated conditions (n=50), presented as box-and-whisker plots. *** indicates p<0.001.
**Suppl. Fig. S4**: miR-375 antagonirs transfected into MCC cells or fibroblasts result in miR-375 knockdown

a- c: miR-375 antagonirs 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 antagonirs were transfected into MRC-5 and Fibro 1.12 cells using lipo-fectamine. 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

**MRC-5**

(a) Bar chart showing relative miR-375 expression levels in MRC-5 cells treated with different conditions. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

(b) Western blot images showing α-SMA and β-Tubulin protein levels in MRC-5 cells. The blots are for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

**Fibro 1.12**

(c) Bar chart showing relative miR-375 expression levels in Fibro 1.12 cells treated with different conditions. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

(d) Western blot images showing α-SMA and β-Tubulin protein levels in Fibro 1.12 cells. The blots are for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

(e) Bar chart showing relative mRNA expression levels of ACTA2, CXCL2, and IL1B in MRC-5 cells. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

(f) Bar chart showing relative mRNA expression levels of ACTA2, CXCL2, and IL1B in Fibro 1.12 cells. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

**Fibro 1.12**

(g) Bar chart showing relative TP53 mRNA expression levels in Fibro 1.12 cells. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

(h) Bar chart showing relative TP53 mRNA expression levels in Fibro 1.12 cells. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

(i) Bar chart showing relative RBPJ mRNA expression levels in Fibro 1.12 cells. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.

(j) Bar chart showing relative RBPJ mRNA expression levels in Fibro 1.12 cells. The chart includes bars for 'Alone', 'WaGa-NC', 'WaGa-375kd', 'PeTa-NC', and 'PeTa-375kd'.
Suppl. Fig. S5: miR-375 antagonirs 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 antagonirs 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.