**Extended Data legends**

**Extended Data Fig. 1. Host ATF4 deletion causes a transient weight loss and gender-independent increase in survival of B16F10 cells-injected mice. a**, Genotyping of mice for Rosa26::CreERT2 and ATF4 status. **b**, qRT-PCR of ATF4 in spleen (n = 4 per group). Values represent mean + SEM, unpaired t-test. **c**, Reversible BW loss post ATF4 excision (n = 10-14 per group); n.s. = not significant. Values represent mean + SEM, unpaired t-test. **d**, Schema for injection of tumor cells post tamoxifen treatment. **e**, Tumor growth curves of single mouse plotted from B16F10 cells-injected mice. **f**, Kaplan-Meier survival analysis by gender from E. Log-rank (Mantel-Cox) test. **g**, Tumor growth curves of single mouse plotted from MH6419 cells-injected mice.

**Extended Data Fig. 2. Reduction of markers of activation and collagen-associated genes in CAFs cluster. a**, Schematic for harvesting B16F10 tumors at smaller (150 mm3) and larger (300 mm3) volumes and processing for scRNA-seq. **b**, scRNA-seq on small size B16F10 tumors. Violin plots showing the expression of ATF4 across all clusters. **c**, Bar plot displaying the normalized Log2 fold change of cell types in each cluster. **d**, UMAP plot of re-clustered CAFs showing the vCAFs signature. **e**, scRNA-seq on large size B16F10 tumors. Dot plot displaying selected gene markers across all clusters. The color intensity represents the average expression while the size of dots indicates the percentage of cells expressing each gene. **f**, Violin plots showing the expression of ATF4 across all clusters. **g**, Bar plot displaying the normalized Log2 fold change of cell types in each cluster. **h**, Bar plot displaying the eight most significant Reactome pathways enriched in *Atf4*wt/wt CAFs using the genes upregulated in *Atf4*wt/wt. **i**, Dot plot displaying selected gene markers across CAFs subclusters. **j**, UMAP plot of re-clustered CAFs showing the melCAFs signature and **k**, the vCAFs signature. **l**, Violin plots showing the expression of *Acta2* and *Pdgfrb* in CAFs subclusters. **m**, UMAP plot of re-clustered CAFs from merged small and large volume B16F10 tumors. **n**, vCAFs signature on merged CAFs UMAP plot.

**Extended Data Fig. 3. ATF4 loss is associated with abnormal vascularization, reduced collagen deposition and extensive intratumoral necrosis. a**, Quantification of the microvascular density in sections from B16F10 tumors (n = 4 per group). Values represent mean + SEM, unpaired t-test. **b**, Representative IF images from MH6419 tumors (appr. 300 mm3) stained for CD31 (green). Original magnification, 10x, 28x (insets). **c**, Quantification of the microvessel length (in mm) (left) and microvascular density (n = 4 per group) (right) from B. Values represent mean + SEM, unpaired t-test. **d**, Representative IF images from B16F10 tumors (appr. 1000 mm3 ) stained for CD31 (green). Original magnification, 10x, 28x (insets). **e**, Quantification of the microvessel length (in mm) from D (n = 4 per group). Values represent mean + SEM, unpaired t-test. **f**, Representative IF images from B16F10 tumors stained for Hoechst only. The yellow highlighted area indicates tumor necrosis. **g**, Quantification of the ratio of tumor necrotic area over the total tumor area from F (n = 5 per group). **h**, Flow cytometric analysis and quantification of the % dead cells in B16F10 tumors (n = 3-5). Values represent mean + SEM, unpaired t-test. **i**, Quantification of the % of aSMA+CD31+/CD31+ in B16F10 tumors (n = 3-4). **j**, Representative IF images from MH6419 tumors stained for CD31 (green) and aSMA (red). Magnification, 10x. **k**, Quantification of the % aSMA positive area from J (n = 4 per group). Values represent mean + SEM, unpaired t-test. **l**, Quantification of the % of aSMA+CD31+/CD31+ from J (n = 4 per group). Values represent mean + SEM, unpaired t-test. **m**, Confocal microscopy on B16F10 tumors co-stained for CD31 (green) and aSMA (red). **n**, Representative IF images from B16F10 tumors stained for CD31 (green) and PDGFRb (red). Magnification, 10x. **o**, Quantification of the % PDGFRb positive area from N (n = 4 per group). Values represent mean + SEM, unpaired t-test. **p**, Quantification of the % of PDGFRb+CD31+/CD31+ from N (n = 4-6 per group). Values represent mean + SEM, unpaired t-test. **q**, Representative images from MH6419 tumor sections stained with an antibody against collagen (green). **r**, Quantification of the % of positive collagen area from Q (n = 4-7 per group). Values represent mean + SEM, unpaired t-test. Scale bars, 100 mm (B, D, J, N) and 1mm (F and Q).

**Extended Data Fig. 4. ATF4 loss reduces intracellular and secreted collagen and impairs proliferative capability in LFBs and DFBs. a**,qRT-PCR of ATF4 and ASNS in DFBs (n = 4-5 per group). Values represent mean + SEM, unpaired t-test. **b**, Genotyping of mice for Col1a1::CreERT2 and ATF4 status. **c**, qRT-PCR of Col1a1, Col1a2 and ASNS in LFBs (n=4-7 per group). Values represent mean + SEM, unpaired t-test. **d**, qRT-PCR of Col1a1 in DFBs (n = 4-5 per group). Values represent mean + SEM, unpaired t-test. **e and f**,LC-ESI-MS/MS analysis to measure the precursor serine-13C3 and glutamine-13C515N2 and the metabolic flux from serine to glutathione in LFBwt/wt and LFBD/D cells (n = 3 per group). Values represent mean + SEM. # and & indicate a statistically significant change from the LFBwt/wt at each isotopologue (# p<0.001, & p<0.01). **g**, Proteins were detected by immunoblotting in untreated DFBs. b-actin was used as a loading control. **h**, Representative images of collagen deposition from DFBwt/wt and DFBD/D using second harmonic generation (SHG) microscopy. **i**, Quantification of the fluorescent signal from H. Values represent mean + SEM, unpaired t-test. **j**, Representative images from EdU pulsed LFBwt/wt and LFBD/D cells. **k**, Quantification of % EdU+ pulsed LFBwt/wt and LFBD/D cells by flow cytometry (n = 5-6 per group). Values represent mean + SEM, unpaired t-test. Scale bars, 100 mm. **l**, Representative images from EdU pulsed DFBwt/wt and DFBD/D cells. **m**, Quantification of % EdU+ cells from L. Values represent mean + SEM, unpaired t-test. Scale bars, 100 mm.

**Extended Data Fig. 5. Reduced sprouting and tube formation of ECs treated with CM from LFBD/D. a**, Flow cytometry to confirm the purity of the isolated lung ECs (pre = pre magnetic beads separation; CD31-, the negative fraction of beads; CD31+, the positive fraction of beads). **b**, qRT-PCR of ASNS in ECwt/wt and ECΔ/Δ (n = 2 per group). Values represent mean + SEM, unpaired t-test. **c**, ECwt/wt and ECΔ/Δ were treated with CM collected from LFBwt/wt or LFBD/D and plated for tube formation assay and analyzed 8h after plating. Quantification of the average number of sprouts and tubes per field. Values represent mean + SEM, unpaired t-test.

**Extended Data Fig. 6. A positive correlation between the ATF4 target signature and COL1A1, ACTA2, PDGFRb and FAP in multiple human tumors. High ATF4 levels correlate with increased COL1 expression on human melanoma tumors. a**, Pearson correlation between the fibroblast ATF4 target signature and COL1A1, ACTA2, PDGFRb and FAP in Brain Lower Grade Glioma (LGG), Kidney renal papillary cell carcinoma (KIRP), Kidney renal clear cell carcinoma (KIRC) and Bladder urothelial carcinoma (BLCA). The linear regression lines along with 95% confidence intervals (shaded regions) are shown. **b**,Representative images from immunohistochemical staining for COL1 and ATF4 of human melanoma tissues and **c**, human pancreatic adenocarcinoma tissues. **d**, Human melanoma tissue arrays containing sections from 176 tumors and 16 healthy controls were stained for COL1 (upper panel) and ATF4 (lower panel) proteins. Damaged or tissues expressing high melanin levels were excluded from the quantification. Red and green boxes indicate representative high and low expression levels of COL1 and ATF4, respectively. **e**, Pearson correlation between the % ATF4 area and % COL1 area in primary (upper) and metastatic (lower) groups from the human melanoma tissue array in D.

**Extended Data Fig. 7. High ATF4 levels correlate with increased COL1 expression on pancreatic adenocarcinoma tumors. High levels of COL1A1 are associated with poor overall survival in multiple human tumors. a**, Pancreatic adenocarcinoma tissue array containing sections from 24 tumors were stained for COL1 (upper panel) and ATF4 (lower panel) proteins.

**b**, Pearson correlation between the % ATF4 area and % COL1 area in all samples and **c**, in grade 2 (upper) and grade 3 (lower) groups. **d**, Kaplan-Meier plot of survival time of PAAD (n=57), LGG (n=168), KIRP (n=94), KIRC (n=172) and BLCA (n=132) patients with high or low COL1A1 expression. Log-rank (Mantel-Cox) test.