Supplementary Materials and Methods

Instrument settings for MethySYBR PCR

Each PCR reaction contained 12.5 µl 2× PowerUp SYBR Green Master Mix (Life Technology), 80 nM of forward and reverse primers and 5 ng of DNA template in a total volume of 25 µl. The PCR program consisted of initial denaturation (95°C, 10 min), 45 cycles of denaturation (95°C, 15 s), annealing/extension (60°C, 1 min), and an extra incubation step of 77°C (for SOCS1) or 72°C (for ALU) for 30 s to diminish the artifact caused by primer dimerization. The primer sequences are summarized in Supplementary Table S1.

Pryosequencing primers and targeted sequence

SOCS1 methylation analysis by pyrosequencing of bisulfie-converted DNA was performed on a Pyromark Q24 system (Qiagen). Bisulfite converted DNA was amplified with a biotinylated primer pair (Table S1). The methylation levels of the amplified non-biotinylated strand were analyzed using a sequencing primer. The targeted sequence of *SOCS1* is 5'-CTGCGTGCACGGCGGGCGCTGCCGG-3'.

Instrument settings for immunofluorescence

Panc10.05 tumor cells were cultured in the 8µm-pore inserts of the trans-well system. MSCs were cultured on cover slips placed in the bottom chamber. After co-culturing for 5 days, MSCs on the cover slips were fixed in 4% paraformaldehyde for 15 min at room temperature, and then

permeabilized for 15 min in PBS containing 0.4% Triton X-100. Next, the cover slips were incubated for 1 hour with 10% goat serum in PBS containing 0.1% Triton X-100 . The cover slips were subsequently co-stained with a FITC-conjugated mouse anti-human pan-Cytokeratins monoclonal antibody (EMD Millipore, C-11) at a 1:200 dilution and a PE-conjugated mouse anti-human STAT3 monoclonal antibody (BD Biosciences, M59-50) or a PE-conjugated mouse anti-human phosphorylated STAT3 (pY705) monoclonal antibody (BD Biosciences, 4/P-STAT3) at a 1:100 dilution for 1 hour at room temperature followed by washes in PBS with 0.5% NP-40. Cells were mounted and counterstained with DAPI. Images were captured at a 20× magnification using a Nikon microscope.

Instrument settings for SOCS1 Immunohistochemistry

Immunohistochemistry for SOCS1 was performed manually as described by Komazaki et al. 2004(41). After deparaffinization and hydration of tissue, heat-induced antigen retrieval was performed in citrate buffer (pH 6.0) using a pressure cooker at 125°C for 30 s and 95°C for 10 s. Incubation with rabbit antibodies against SOCS1 (Santa Cruz) at 1:50 followed by biotinylated secondary goat antibodies against rabbit IgG (Vector) at 1:200 dilution for 30 min. After incubation with ABC Vectastain (Vector), the reaction was developed using the DAB substrate (Vector Labs). All stains were counterstained with hematoxylin.

Software program settings for merged analysis of DNA methylation array and gene expression array

Merged analyses of gene expression data and DNA methylation data were performed by the BeadStudio Software (Illumnina). SNP and X/Y chromosomes were excluded. Positive gene

methylations were defined as those with methylation beta values > 0.5. Beta values were defined as intensity ratios between methylated and unmethylated alleles. Genes were considered to be more methylated and also downregulated in MSCs or 09.05CAFs upon co-culturing with PDAC tumor cells comparing to those in the single cultures if their Pearson's correlation coefficiency R score, which reflects the degree of linear relationship between methylation beta and gene expression signal intensity, was smaller than -0.9 and if their methylation beta value in MSCs or 09.05CAFs upon co-culturing with PDAC tumor cells were 0.3 higher than that in MSCs or 09.05CAFs in the single cultures (http://res.illumina.com/documents/products/technotes/technote_gene_expression_methylation_merging.pdf). For this merged analysis, gene expression changes in any magnitude were included. The microarray gene expression data were also analyzed separately for the pathway analysis, where fold of gene expression change either increased or decreased > 1.5 and $p<0.001$ were the statistical parameters used to filter the genes whose expression are significantly altered.