Supplemental Methods.

Cells. PC3 cells (ATCC, Manassas, VA), primary human myoblasts (hMYO) and primary prostate smooth muscle cells (pSMC), both obtained from Lonza, were maintained according to the manufacturer's instructions. Primary murine myoblasts (mMYO) were isolated and grown as described in {Leikina, 2013 #48}. Primary human prostate cancer cells (pPCa) developed from a human prostate adenocarcinoma sample (Gleason 8 (4+4), T2N0M0) were obtained from Celther, Polska (Poland) and cultured according to the manufacturer's instructions. The cells have been characterized by the manufacturer as epithelial cells via morphological observation throughout serial passages and by positive staining for pan-Cytokeratin and for tumor cell specific MUC-1. Based on CD90 staining, the cultures are free of fibroblasts (less than 1%).

Reagents. Recombinant human IL-4 and IL-13 were obtained from Peprotech (catalogue # 200-04 and 200-13). Human IL-4 and IL-13 neutralizing rabbit antibodies were purchased from Cell Signaling (Cat. # 11964) and Abcam (Cat. # Ab9576), respectively. As a negative control for the neutralizing antibodies, we used non-specific IgG (Cell signaling, Cat.# 2729). We used synthetic peptide inhibitor of Syn-1-mediated fusion (Syn-1 peptide, Ac-SGIVTEKVKEIRDRIQRRAEELRNTGPWGL-NH2), described and characterized in {Chang, 2004 #46}, and as a negative control (Syn-1 scr peptide) a peptide with the same amino acid composition but a scrambled sequence (Ac-GKWGLSRIRTELRNTEPVKEQVRAEIGDRI-NH2). Both peptides were custom synthesized by GenScript. In all experiments, peptides were used at a 50 μg/ml concentration

For drug testing, we used doxorubicin hydrochloride from Sigma Cat. # D1515) and cisplatin (cis-diamine platinum (II) dichloride from Sigma Cat. # 479306).

To suppress DNA replication we used DNA methylation inhibitor, 5-Fluoro-2'-deoxyuridine (FdUrd, final concentration of 200 µM, Sigma, Cat. # F0503)

For labeling cells with fluorescent markers, we used CellTracker^{TM} Green CMFDA dye (Thermo Fisher Scientific, Cat# C7025), CellTrace™ Far Red dye (Thermo Fisher Scientific, Cat#C34564) and Hoechst-33342 (Thermo Fisher Scientific, Cat# H3570).

For growing cells in anchorage-independent conditions we used serum-free DMEM/Ham's F-12 (1:1) supplemented with 20-ng/ml EGF (Peprotech), 10-ng/ml bFGF (Peprotech), 0.4 % BSA (Sigma), 5-µg/nl insulin (Sigma) and 1x N2 Supplement A (Stem Cell Technologies).

Plasmids. Syn1-4 shRNA and non-target scramble shRNA were obtained as a set (Cat. # TL307608) from Origene. Plasmid pHCMV HERV-Hyper-W expressing Syn1 mutant (Syn1f) with C-terminal truncations that increases the fusogenicity of the protein {Drewlo, 2006 #120} was a kind gift from Drs. Valery Krizhanovsky, The Weizmann Institute of Science, and Shmuel Rozenblatt, Tel Aviv University.

Virus production and infection. We seeded 293T cells at $3x10^5$ cells per well in 6-well plates and on the next day co-transfected them with a mixture of plasmid DNA containing viral vector and packaging plasmids using Mirus TransIT® -2020 (Mirus). To generate lentiviruses, we co-transfected the packaging plasmids (pCMV-VSVG and psPAX2) with Syn1 shRNA vector or non-target shRNA into 293T cells. For viral infection, we seeded the cells at 50% confluence in

6-well plates. On the next day, we mixed virus-containing supernatants from 293T cultures with polybrene at a final concentration of 4 µg/ml. The plate was centrifuged at 2,000 rpm for 1 h at 35°C and was subsequently returned to the cell culture incubator. Cells infected with lentiviruses were selected with puromycin (1 µg/ml) at 48 h after infection.

RNA isolation, reverse transcription, and qPCR analysis. RNA was extracted with the RNeasy Plus mini kit (Qiagen) for muscle and cancer cells. cDNA was synthesized by random priming from 1 µg of total RNA with the Q-Script cDNA super mix kit (Quanto biology), according to the manufacturer's protocols. Primers for qPCR analysis were synthesized by Eurofins Scientific. We performed qPCR using *PerfeCTa SYBR Green FastMix* (Bio-Rad), according to the manufacturer's protocol. We analyzed data, determining quantities of gene-specific mRNA expression, using the comparative CT method, as described previously [36]. CT refers to the "threshold cycle" and is determined for each experiment with MyiQ software. Amplification of GAPDH was performed for each reverse-transcribed sample as an endogenous quantification standard. The primers were as follows:

Syn1

5'-ATGGAGCCCAAGATGCA--3'
5'-AGATCGTGGGCTAGCAG-3'
5'-AACTGCAAGCAACTGGGTCT-3'

AnxA5

5'-GCTCAAGCCTGGAAGATGAC-3'
5'-TCGTGTTCCAAAGATGGTGA-3'

GAPDH

5'-ATTGACCTCAACTACATGGTTTACATG-3'
5'-TTGGAGGGATCTCGCTCCTGGAAG-3'

IL4

5'-TGCATCGTTAGCTTCTCCTG-3'
5'- CTGCTCTGTGAGGCTGTTCA-3'

IL13

5’- ATCCTCTCCTGTTGGCACTG-3’
5’- CAGGTTGATGCTCCATACCA-3’

CD133

5’-GGCCATCCAAATCTGTCCTA-3’
5’-CAGTCTGACCAGCGTGAAAA-3’

Western-blot analysis. Cells were lysed in cell lysis buffer: 0.5% Triton X-100, 20 mM Tris, 100 mM NaCl, 1 mM EDTA, 1 mM beta glycerophosphate (Boston BioProducts), and 1 mM sodium orthovanadate (Boston BioProducts), supplemented with 1 ml of protease inhibitor cocktail (Sigma). The lysate was transferred into an Eppendorf tube, sonicated for 10 s, and centrifuged for 10 min at 15,000 rpm and 4ºC. The soluble fraction of the lysate was added to the denaturing sample buffer (Boston BioProducts), boiled, loaded onto a 4–12% Mini Protean TGX gel (Bio-Rad), and separated with SDS-PAGE. We transferred the separated proteins to a PVDF membrane (Bio-Rad) using the Bio-Rad Trans-blot turbo transfer system. After the transfer, the membrane was blocked with 5% nonfat dry milk dissolved in PBS containing 0.05% Tween 20 (Bio-Rad). The membrane was incubated with the primary antibodies at 4 ºC overnight. After incubation, the membrane was washed three times with PBS containing 0.05% Tween 20 and then incubated with alkaline phosphatase–conjugated secondary antibody (Thermo Fisher Scientific). The membrane was washed three times with PBS containing 0.05% Tween 20, and the protein bands were visualized with enhanced chemifluorescence (ECF reagent; GE Healthcare). As primary antibodies, we used the following antibodies: to Syn1 (Abcam, Cat. # Ab179693); to AnxA5 (Abcam, Cat. # Ab14196); to pAKT-Ser 473 (Cell signaling, Cat. # 4060); to Vimentin (Cell Signaling, Cat. # 5741); to E-cadherin (Cell Signaling, Cat. # 3195); to MMP-9 (Cell Signaling, Cat. # 13667), to Slug (Anaspec, Cat. # 54625); to PTEN (Sigma, Cat#P3487); to P53 (Cell signaling, Cat# 9282); to androgen receptor (AR) (Cell signaling, Cat# 5153) and, as a loading control, antibodies to tubulin (Sigma, Cat. # T0926).

Silencing of Annexin A5 expression. Universal scrambled negative control siRNA was obtained from Origene (Cat# SR30004) and siRNA targeting human Anx A5 was obtained from Santa Cruz (Cat # SC-29686). Both Anx A5 siRNA and negative control siRNA transfections were performed at 200 pM per 35 mm plate using Trans-IT transfection reagent (Mirus, Cat# MIR5400) according manufacturer recommendations.

Flow Cytometry. Cells were detached with 4 µmol EDTA at RT for 5 min. Cells were washed in PBS and then centrifuged at 1,000 rpm (Beckman Coulter rotor number 4250). Nonspecific binding sites were blocked in blocking buffer (2% serum in PBS) at 4°C for 30 min. Then the cells were incubated with or without (control) CD133-PE antibody (Miltenyi, Catalog # 130080801), as recommended by the manufacturer, in the blocking buffer at 4°C for 30 min. Cells were washed twice with PBS. The surface expression of CD133-PE was analyzed with the FACS Calibur flow cytometry system (BD Biosciences) or the Miltenyi Biotec Flow Cytometer. Live and dead cells were distinguished with either cell dead stain (Life technologies, Cat. # L10119) or DAPI staining. Flow cytometry data for live cells was analyzed with FlowJo Version 10.

Drug resistance. Cancer cells on cell culture inserts had been co-cultured with muscle cells for 72 h, seeded in 96-well plates at $20x10^3$ cell/well density, and the next day, cells were treated with different concentrations of doxorubicin or cisplatin for 24 h. Metabolic activity of the drug-treated cells was analyzed with the colorimetric MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay using the Vybrant MTT cell proliferation assay kit from Thermo Fisher Sci (Cat. # V13154). Basically, the cells were seeded in 96-well plates and, 24h later, the medium was replaced with 100 µL of fresh culture medium.

To each well, 10 µL of the 12 mM MTT stock solution was added. In the negative control, we added 10 µl of the MTT stock solution to 100 µL of medium in a cell-free well. After a 4-h incubation at 37°C for 4 hours, 85 µl of medium was removed and 50 µL of DMSO was added into each well and mixed thoroughly with the pipette. After a 10-min incubation at 37°C for 10 minutes we measured the absorbance of the samples at 540 nm.

In another approach, we analyzed drug resistance of the cancer cells co-cultured with muscle cells or treated with IL-4/IL-13 by counting viable cancer cells. In this approach, cancer cells were co-cultured with muscle cells; or treated with either IL-4 or IL-13; or placed into conditioned medium from PC3 cells co-cultured for 72h with either mMYO, hMYO or pSMC for 72 h. For the last 24-h of the cell incubation, the cells, still in the presence of the cytokines or in the conditioned medium, were treated with either doxorubicin or cisplatin. At the end of the 24h of drug treatment, we counted trypan-blue excluding cells.

Cytokine expression assays. Human IL-4 and IL-13 ELISA kits were obtained from Thermo Fisher Sci (Cat. # KHC0041 and Cat. # KHC0131, respectively). Mouse IL-4 and IL-13 ELISA kits were also purchased from Thermo Fisher Sci (Cat. # EMIL4 and Cat. # BMS6015). Conditioned cell culture medium was collected and centrifuged. Then, 100 µl of sample or control (or standard) was analyzed following the manufacturer's protocol. We measured the optical density (OD) of each well within 30 min, using a microplate reader set to 450 nm. a standard curve was plotted based on OD values of recombinant IL-4 or IL-13. We averaged the triplicate readings for each standard, control, and sample and subtracted the average zero standard optical density. We prepared a standard curve by plotting the mean absorbance for each standard on the y-axis against the concentration on the x-axis. The best fit line through the points

on the graph was plotted by regression analysis. IL-4/IL-13 concentrations were calculated based on the standard curve for each sample.

Immunohistochemistry staining of paraffin embedded tissue slices. Briefly, after citrate buffer antigen retrieval, the sections were blocked in 2% BSA/10% normal goat serum for 30 minutes at room temperature. Primary antibodies were added in 2% BSA/PBS and incubated overnight at 4°C. The following day, cells were thoroughly washed and fluorescently labeled by a secondary antibody (in 2% BSA/PBS) for 1 hour at room temperature in the dark. DAPI was added to label the nuclei, and cells were mounted using DAKO fluorescent mounting media. Images were taken using confocal microscopy with equal exposure times to allow for further analysis using ImageJ software. 10 images per sample were analyzed. We used Image J to analyze fluorescent intensity of the images. We used a script to exclude any tissue-free spaces in the images and total fluorescent intensity was normalized by the total area of the tissue in the field of view. Note that in our analysis we do not distinguish cells of different types and further analysis is needed to correlate the expression of Syn1 and Anx A5 in individual cells in cancer tissues and in non-malignant tissues with expression of specific markers characteristic for different cell types. Procedures using human tissue were approved by the Institutional Review Board and conducted in compliance with ethical and safe research practices involving human subjects or tissues.

Time-lapse microscopy. A mix of PC3 cells expressing and not expressing GFP were co-plated with hMYO on 35 mm ibiTreat μ-dishes (ibidi, Germany) and co-incubated for 48h before imaging. Cell nuclei were labeled with SiR-DNA Kit (Spirochrome, USA) immediately before imaging according to manufacturer's recommendations. Live-cell imaging was performed at 37^0C in closed DH-40iL culture

dish microincubator (Warner Instruments, USA). Level of CO_2 was maintained at 5% by continuous supply of 95/5 Air/CO_2 gas mixture. Images were acquired every 5 minute using appropriate fluorescence filters (Semrock, USA) on pco.edge 5.5 sCMOS camera (PCO AG, Germany) controlled by micro-manager 1.4.23 software. Optical setup included AxioObserver.D1 microscope (Zeiss, Germany) equipped with Plan Apochromat 10x /0.45 Ph1 lens (Zeiss, Germany), pE-2 LED illumination system (CoolLED, UK) and motorized emission filter wheel (LUDL, USA).