Supplementary Information

Molecular signatures of mu opioid receptor and somatostatin receptor 2 in pancreatic cancer

Raphael Jorand, Sunetra Biswas, Devin L. Wakefield, Steven J. Tobin, Ottavia Golfetto, Kelsey Hilton, Michelle Ko, Joe W. Ramos, Alexander R. Small, Peiguo Chu, Gagandeep Singh and Tijana Jovanovic-Talisman
Supplementary Figure S1. Distribution of endogenous MOR, SSTR2, and CXCR4 in PANC-1 cells. (A) Using dSTORM, MOR was imaged in PANC-1 cells. MOR was detected using a selective primary antibody and an Alexa Fluor 647 tagged secondary antibody; scale bar, 5 µm. A magnified region is given in the bottom right (lined in cyan); scale bar, 500 nm. A blocking peptide control is given in the upper right (lined in magenta); scale bar, 5 µm. (B) Using dSTORM, SSTR2 was imaged in PANC-1 cells. SSTR2 was detected using a selective primary antibody and an Alexa Fluor 647 tagged secondary antibody; scale bar, 5 µm. A magnified region is given in the bottom right (lined in cyan); scale bar, 500 nm. A blocking peptide control is given in the upper right (lined in magenta); scale bar, 5 µm. (C) Using dSTORM, CXCR4 was imaged in PANC-1 cells. CXCR4 was detected using a selective primary antibody and an Alexa Fluor 647 tagged secondary antibody; scale bar, 5 µm. A magnified region is given in the bottom right (lined in cyan); scale bar, 500 nm. A blocking peptide control is given in the upper right (lined in magenta); scale bar, 5 µm. (D) Schematic representation of the sequence overlay for human MOR, SSTR2, and CXCR4. The blocking peptide sequence (C-terminus for MOR and SSTR2; N-terminus for CXCR4) is boxed. For SSTR2, only the region of the sequence where blocking peptide is found is disclosed and highlighted.

Normalized Gaussians are shown throughout. We confirmed that we were imaging cells using a transmission light source. Identical imaging and processing conditions were used. Colors were inverted for clarity.
Supplementary Figure S2. Knockdowns of CXCR4, MOR, and SSTR2 in PANC-1 cells confirm antibody specificity. (A) Western blot images confirm that CXCR4 is largely absent in PANC-1/CXCR4si cells; MOR is largely absent in PANC-1/MORsi cells; and SSTR2 is largely absent in PANC-1/SSTR2si cells. Other PANC-1 derived cell lines have unperturbed levels of the three GPCRs. Full blots are shown in Supplementary Fig. S13C. (B) As compared to levels in parental PANC-1 cells, the relative amounts of CXCR4, MOR, and SSTR2 mRNA were determined in PANC-1 derived cells. Results were obtained from three independent experiments, each done in triplicate. CHO-S cells were used as negative controls and MCF-7 cells as positive controls. Results are expressed as the average with standard deviation. (C) CXCR4, MOR, and SSTR2 were detected with selective primary and Alexa Fluor 647 tagged secondary antibodies in PANC-1 NS control cells. Magnified regions are shown; scale bar, 2 μm. PANC-1/CXCR4si, PANC-1/MORsi, and PANC-1/SSTR2si cells show no appreciable antibody binding (corresponding insets, scale bar 5 μm). Normalized Gaussians are shown throughout. Identical imaging and processing conditions were used. Colors were inverted for clarity.
Supplementary Figure S3. Distribution of SSTR2 and MOR in pancreatic cells. (A) The distribution of SSTR2 (cyan, detected with Alexa Fluor 647) and MOR (magenta, detected with Atto 488) was determined in normal pancreatic cells. (B) The distribution of SSTR2 (cyan, detected with Alexa Fluor 647) and MOR (magenta, detected with Atto 488) was determined in PANC-1 cells. Overlap is evident in dark blue. Scale bar for full areas (top panels), 5 μm. Scale bar for magnified areas (middle and bottom panels), 100 nm. Top panel, all peak centers detected by NIS-Elements are shown; middle panel, peak centers detected by NIS-Elements are shown; erode function in ImageJ was used to make peaks more visible. Bottom panel, normalized Gaussian rendering is shown. Identical imaging and processing conditions were used. Colors were inverted for clarity.
Supplementary Figure S4. Two color imaging: MOR/SSTR2 and MOR/CXCR4 in PANC-1 MCTS. (A) The distribution of SSTR2 (magenta, detected with Atto 488) and MOR (cyan, detected with Alexa Fluor 647) was determined in a region of PANC-1 MCTS. Overlap is evident in dark blue; scale bar, 2 μm. (B) Prior to dSTORM imaging, MOR and SSTR2 blocking peptides along with the respective primary antibodies were applied to PANC-1 MCTS. Subsequently, labeled secondary antibodies were used as before and two-color imaging was performed. Negligible fluorescence is observed with blocking peptides; scale bar, 5 μm. (C) The distribution of CXCR4 (magenta, detected with Atto 488) and MOR (cyan, detected with Alexa Fluor 647) was determined in a region of PANC-1 MCTS; scale bar, 2 μm. (D) Prior to dSTORM imaging, MOR and CXCR4 blocking peptides along with the respective primary antibodies were applied to PANC-1 MCTS. Subsequently, labeled secondary antibodies were used as before and two-color imaging was performed. Negligible fluorescence is observed with blocking peptides; scale bar, 5 μm.

We confirmed that we were imaging MCTS using a transmission light source. Identical imaging and processing conditions were used. Peak centers, detected by NIS-Elements, are shown throughout; erode function in ImageJ was used to make peaks more visible. Colors were inverted for clarity.
Supplementary Figure S5. GPCR cluster sizes and circularity obtained using SR-Tesseler (Levet et al., 2015). (A) MOR cluster radius in normal pancreatic cells (top, N=21 cells); cancerous PANC-1 cells (middle, N=22 cells); PANC-1 MCTS (bottom, N=21 cells). MOR was detected with either Atto 488 or Alexa Fluor 647. (B) SSTR2 cluster radius in normal pancreatic cells (top, N=21 cells); cancerous PANC-1 cells (middle, N=22 cells); PANC-1 MCTS (bottom, N=21 cells). SSTR2 was detected with either Atto 488 or Alexa Fluor 647. (C) CXCR4 cluster radius in normal pancreatic cells (top, N=13 cells); cancerous PANC-1 cells (middle, N=13 cells); PANC-1 MCTS (bottom, N=14 cells). CXCR4 was detected with Atto 488. (D) Average cluster radius and cluster circularity for MOR, SSTR2, and CXCR4; * denotes p≤0.02. (E) MOR cluster radius in normal tissue (top, N=17 cells) and cancerous tissue (bottom, N=19 cells) from 3 patients. (F) SSTR2 cluster radius in normal tissue (top, N=17 cells) and cancerous tissue (bottom, N=19 cells) from 3 patients. (D) Average cluster radius and cluster circularity for MOR and SSTR2 in patient samples; * denotes p≤0.02.
Supplementary Figure S6. Choice of label does not influence co-localization between MOR and SSTR2. (A) Cross-correlation curves show co-localization between MOR and SSTR2 in PANC-1 cells: for the dark gray diamonds, MOR was detected with Alexa Fluor 647 while SSTR2 was detected with Atto 488 (N=19 regions from 10 cells); for the light gray diamonds, MOR was detected with Atto 488 while SSTR2 was detected with Alexa Fluor 647 (N=22 regions from 12 cells). (B) Cross-correlation curves show co-localization between MOR and SSTR2 in PANC-1 MCTS: for the dark red triangles, MOR was detected with Alexa Fluor 647 while SSTR2 was detected with Atto 488 (N=19 regions from 11 MCTS); for the light red triangles, MOR was detected with Atto 488 while SSTR2 was detected with Alexa Fluor 647 (N=21 regions from 10 MCTS). (C) Cross-correlation curves show no co-localization between MOR and SSTR2 in normal pancreatic epithelial cells: for the dark blue circles, MOR was detected with Alexa Fluor 647 while SSTR2 was detected with Atto 488 (N=15 regions from 8 cells); for the light blue circles, MOR was detected with Atto 488 while SSTR2 was detected with Alexa Fluor 647 (N=36 regions from 13 cells).

In all cases no long-range correlations were observed. Error bars represent standard error of the mean (s.e.m.); region area size, 80 μm². For both color combinations, 1) MOR and SSTR2 had significantly lower density (p<0.05) in normal pancreatic cells compared to PANC-1 cells; 2) SSTR2 had significantly lower density (p<0.05) in PANC-1 MCTS compared to PANC-1 cells.
Supplementary Figure S7. Cross-correlation analysis is robust. Cross-correlation curves were obtained from Monte-Carlo simulations. In all cases we simulated two channels: one generated with receptor R in red and another generated with receptor G in green. We then computed a cross-correlation curve from the image with R and G combined assuming different antibody binding efficiencies and receptor densities. In all cases the cross-correlation curve equaled 1 when no heterodimers were present; the cross-correlation curves were greater than 1 when we had 5%, 10%, or 30% heterodimers. We assumed the following hypotheses, which operate under eight different cases: (A) The densities of R and G were equal to 20 receptors per µm²; 50% of the receptors were labeled (10 receptors detected in each channel per µm²). No homodimers (RR and GG) were present. Averaged number of appearances was 8 for both channels. (B) The densities of R and G were equal to 20 receptors per µm²; 50% of the receptors were labeled (10 receptors detected in each channel per µm²). No homodimers (RR and GG) were present. Averaged number of appearances was 6 and 2 for R and G channels, respectively. (C) The densities of R and G were equal to 20 receptors per µm²; 50% of the receptors were labeled (10 receptors detected in each channel per µm²). No homodimers (RR and GG) were present. Averaged number of appearances was 4 for both channels. (D) The densities of R and G were equal to 50 receptors per µm²; 20% of the receptors were labeled (10 receptors detected in each channel per µm²). No homodimers (RR and GG) were present. Averaged number of appearances was 4 for both channels. (E) The densities of R and G were equal to 20 receptors per µm²; 50% of the receptors were labeled (10 receptors detected in each channel per µm²). Receptors that were not involved in heteromerization were organized as either monomers or homodimers with equal probability; i.e. 50% monomers (R and G) and 50% homodimers (RR and GG). Averaged number of appearances was 4 for both channels. (F) The density of R was equal to 20 receptors per µm²; 50% of the receptors were labeled. The density of G was equal to 50 receptors per µm²; 20% of the receptors were labeled (10 receptors detected in each channel per µm²). No homodimers (RR and GG) were present. Averaged number of appearances was 4 for both channels. (G) The densities of R and G were equal to 8 receptors per µm²; 50% of the receptors were labeled (4 receptors detected in each channel per µm²). No homodimers (RR and GG) were present. Averaged number of appearances was 4 for both channels. (H) The densities of R and G were equal to 20 receptors per µm²; 20% of the receptors were labeled (4 receptors detected in each channel per µm²). No homodimers (RR and GG) were present. Averaged number of appearances was 4 for both channels.
Supplementary Figure S8. Representative H&E staining of patient samples (matching healthy and cancer tissue) used for imaging. Experiments were performed at the City of Hope Pathology Core. Magnification, 200x.

Supplementary Figure S9. Keratin 8 and 18 labels epithelial cells and tissues. (A) Keratin 8 and 18 was detected in PANC-1 cells using an Alexa Fluor 405 labeled secondary antibody; scale bar, 5 μm. (B) There was no cross-talk between 405 and 488/647 channels in tissue samples. Keratin 8 and 18 was detected using selective primary and Alexa Fluor 405 tagged secondary antibodies; MOR and SSTR2 were not affinity labeled. Two-color dSTORM imaging using 488 and 647 lasers was performed first (bottom); subsequently, images were acquired with a 405 laser (top). No appreciable 488/647 signal was observed; scale bar, 5 μm. When Keratin 8 and 18 was not affinity labeled, while MOR and SSTR2 were affinity labeled (using selective primary antibodies and Alexa Fluor 647 and Atto 488 labeled secondary antibodies), no signal from epithelial cells in tissue samples was observed in the 405 channel.
Supplementary Figure S10. Confocal images of MOR and SSTR2 in PANC-1 cells in steady state and upon co-activation with agonists. (A) In the absence of agonist, MOR and SSTR2 were predominantly localized on the plasma membrane with appreciable co-localization. (B) Addition of combined agonist resulted in MOR and SSTR2 receptor internalization. Gray scale images are shown on the bottom. Scale bars, 10 μm.
Supplementary Figure S11. Localization of pERK1/2 upon agonist treatment. Confocal imaging was used to determine pERK1/2 localization in cells upon various agonist treatments for the indicated periods of time. pERK1/2 was detected using a selective primary antibody with an Alexa Fluor 647 labeled secondary antibody while the nucleus was detected with DAPI (two channels are shown separately); scale bars, 10 μm. (A) PANC-1 cells were treated with 10 nM dermorphin; 10 nM L-054,264; or 10 nM dermorphin with 10 nM L-054,264 for 3 or 30 min. (B) Normal pancreatic cells were treated with 10 nM dermorphin; 10 nM L-054,264; or 10 nM dermorphin with 10 nM L-054,264 for 3 or 30 min. (C) PANC-1 NS (top), PANC-1/MORsi (middle), and PANC-1/SSTR2si (bottom) cells were treated with 10 nM dermorphin and 10 nM L-054,264 for 3 min. Cells were turboGFP positive. (D) PANC-1 cells were treated with 100 ng/ml CXCL12 or 100 ng/ml CXCL12 with 10 nM dermorphin for 3 or 30 min. (E) Untreated PANC-1 cells (top) and normal pancreatic cells (bottom). (F) Left, validation of PANC-1/β-arrestin2si cells with western blots; Full blots are shown in Supplementary Fig. S13G. Right, PANC-1/β-arrestin2si cells were treated with 10 nM dermorphin and 10 nM L-054,264 for 3 min. Cells were turboGFP positive.
Supplementary Figure S12. Expression of epithelial and mesenchymal markers upon agonist treatment. (A) Combined MOR and SSTR2 agonist treatment did not have a significant effect on mRNA levels of 4 markers in PANC-1/MORsi and PANC-1/SSTR2si cells. Control PANC-1 NS cells have signatures comparable to PANC-1 cells. 10 nM desmopressin and 10 nM L-054,264 were used. Measurements were obtained from three independent experiments, each done in duplicates. Results are expressed as the average with standard deviation. (B) Combined MOR and CXCR4 agonist treatment and CXCR4 agonist treatment did not have a significant effect on mRNA levels of 4 markers in PANC-1 cells. 10 nM desmopressin and 100 ng/mL CXCL12 were used. Measurements were obtained from three independent experiments, each done in duplicate. Results are expressed as the average with standard deviation. (C) Combined MOR and SSTR2 agonist treatment increased protein levels of vimentin and N-cadherin and decreased levels of E-cadherin in PANC-1 cells but not in normal pancreatic cells. Large regions of representative original images are provided in Supplementary Fig. S13H.
Supplementary Figure S13. Western blot quantification and unmodified scans of representative Western blots. (A) Quantification of GPCR protein levels from 3 independent measurements with standard deviation. The blots were quantified using the Biorad-ImageLab software. (B) From Fig. 1B. (C) From Supplemental Fig. S2. (D) Quantification of co-IP blots with standard deviation from Fig. 3D. The blots were quantified using the Biorad-ImageLab software. (E) From Fig. 5A. (F) From Fig 5D. (G) From Supplemental Fig. S11F. (H) From Supplemental Fig. S12C
Supplementary Methods

Primary antibodies.
The antibodies used in assays reported in the paper have all been well characterized for human reactivity in the antibody profile database Antibodypedia and 1DegreeBio. The antibodies used are available through multiple vendors and the references for these particular reagents have been gathered from the database, original manufacturers’ website, and our published work. Primary antibodies include anti-MOR (guinea pig polyclonal, Neuromics, Abcam) (Manzke et al., 2010; Nassirpour et al., 2010; Tobin et al., 2014); anti-SSTR2 (rabbit polyclonal, Neuromics) (Reubi et al., 1998; Reubi et al., 1999); anti-CXCR4 (mouse monoclonal, Neuromics) (Haringman et al., 2006; Pfieffer et al., 2009); anti-phospho-ERK1/2 (Thr202/Tyr204) (rabbit monoclonal, Cell Signaling) (Mark et al., 2008; Chiron et al., 2009); anti-ERK1/2 (rabbit polyclonal, Abcam) (Gertsch et al., 2008; Chen et al., 2009); anti-phospho-EGFR (Tyr1068) (rabbit monoclonal, Cell Signaling) (Katayama et al., 2012; Yoshikawa et al., 2013); anti-EGFR (rabbit monoclonal, Abcam) (Burga et al., 2011; Giles et al., 2013); anti-β-actin (mouse monoclonal, Cell signaling) (Tarassishin et al., 2011; Zheng et al., 2012); anti-cytokeratin 8 & 18 (mouse monoclonal, Cell Marque/Sigma) (Angus et al., 1987; Sasaki et al., 1998); anti-vimentin (rabbit monoclonal, Cell Signaling) (Lacher et al., 2011; Matsuyama et al., 2013); anti-E-cadherin (rabbit monoclonal, Cell signaling) (Kong et al., 2010; Stairs et al., 2011); anti-N-cadherin (rabbit monoclonal, Cell Signaling) (Chen et al., 2013), anti-phospho-p90RSK (Thr573) (rabbit polyclonal, Cell Signaling) (Zaru et al., 2007; Kosako et al., 2009), anti-Na/K ATPase α1(D4Y7E) (rabbit monoclonal, Cell Signaling); Histone H3 (rabbit monoclonal, Cell Signaling) (Wang et al., 2011); anti-β-arrestin2 (rabbit polyclonal) was a kind gift from Dr. J. Benovic(Shankar et al., 2010). Secondary antibodies: Goat Anti-Guinea pig IgG H&L (HRP) (Abcam) (Houl et al., 2006), Goat Anti-Mouse IgG H&L (HRP) (Abcam)(Caci et al., 2015), Goat Anti-Rabbit IgG H&L (HRP) (Abcam) (Janiszewska et al., 2015), Goat anti-mouse (polyclonal, Abcam) (Tammachote et al., 2012), Goat anti-rabbit (polyclonal, Abcam) (KA, 2009), Goat anti-guinea pig (polyclonal, Abcam) (Houl et al., 2006).

RT-PCR primer selection.
For RT-PCR we used:
SSTR2-forward (5’-AAGTCTCTTGGAAATCCGAGT-3’) and
SSTR2-reverse (5’-GAGGACATTCTGGAAAGCTCT-3’) primers (Fujita et al., 1994);
MOR-forward (5’-TCTGGCTCCAAGAAAAGGA-3’) and
MOR-reverse (5’-CAATGCGAGTGCCAGAA-3’) primers (Lu et al., 2013);
CXCR4-forward (5’-GACCGCAACATAGACCACTT-3’) and
CXCR4-reverse (5’-CCGTGGCAAACTGGTACTT-3’) primers (Sun et al., 2014);
Vimentin-forward (5’-TACAGGAAGCTGCTGGAAGG-3’) and
Vimentin-reverse (5’-ACCAGAGGAGTGCAATCCAG-3’) primers (Ma et al., 2016);
E-cadherin-forward (5’-GGCCAGGAAAATCACATCCTA-3’) and
E-cadherin-reverse (5’-GGCAATGTCTCCCTCCAATCC-3’) primers (Li et al., 2015),
N-Cadherin-forward (5’-CTCCATGTGCGCATAGC-3’) and
N-cadherin-reverse (5’-CGATTTCAACAGAGCCTTAC-3’) primers (Woods et al., 2014);
MMP9-forward (5’-GAACCAATCTCACCAGCAGG-3’) and
MMP9-reverse (5’-GCCACCCGAGTGAACATA-3’) primers (Sai et al., 2015)
β-arrestin2-forward (5’-GTCGAGGCTTAACGTCAAG-3’) and
β-arrestin2-reverse (5’-ACAAACACTTTGCGGTCTTC-3’) primers (Jing et al., 2015)
**Knockdowns.**
Each shRNA construct has been bioinformatically verified to match NCBI sequence data: shRNA MOR AntiSense sequence: TTACTTTATGTGTTACTAC, RefSeq NM_001145279; shRNA SSTR2 AntiSense sequence: TAAATGACAAATGTGTTGC, RefSeq NM_001050. shRNA CXCR4 AntiSense sequence: ATCTATGCATAACAGCTG, RefSeq NM_001008540 and NM_003467 β-arrestin2 Antisense sequence: ACCTGGTCACTCTTGTCGARefSeqNM_199004

**MOR, SSTR2, and CXCR4 Tessellation Cluster Analysis.**
Peak localization data (prepared as described in Materials and Methods) was imported to the freely available SR-Tesseler software (Levet et al., 2015). All cell images were analyzed using the same segmentation settings inSR-Tesseler (each color channel data was loadedseparately). Steps to identify clusters in each cell image were carried out as described in the software manual. Briefly, Voronoi diagrams were first applied to the data. Object segmentation was then performed by using a combination of adjusted and default parameters, including the minimum object area (set to 0.01 pixels²), the minimum number of localizations per object (set to 5), and the density factor (set at the default of 2). Receptor cluster data was subsequently extracted from object data using the same parameters. Finally, the cluster data was exported from SR-Tesseler and, using custom code in Matlab, averages were prepared for the results shown in Figure S5.
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