(B) RAGE knockdown increases apoptosis following treatment with oxaliplatin (7 mg/kg) \textit{in vivo}. Included here are representative images of implanted WT (control shRNA) and KD (RAGE shRNA) pancreatic tumors sections that were analyzed by TUNEL assay (green signal). Nuclear staining was done with Hoechst 33342 (blue signal). Inset shows a higher magnification of TUNEL stain.

(C) RAGE knockdown decreases autophagy after treatment with oxaliplatin (7 mg/kg) \textit{in vivo}. Included here are representative images of implanted WT (control shRNA) and KD (RAGE shRNA) pancreatic tumors sections that were analyzed by indirect IF staining of LC3 protein (green signal). Nuclear staining was done with Hoechst 33342 (blue signal). Inset shows a higher magnification of cells following staining with LC3.

\textbf{Figure S1} RAGE is expressed in pancreatic cancer tumor cell lines \textit{in vitro and in vivo}.

(A) RAGE is expressed in pancreatic cancer cell lines. Western blot analysis of RAGE, HMGB1 and actin in several human cancer cell lines is indicated.

(B) RAGE and HMGB1 are expressed in transplantable pancreatic tumor cells \textit{in vivo}. Included here are representative images of implanted pancreatic tumors sections that were analyzed by indirect IF staining of RAGE protein (left, green signal) and HMGB1 (right, green signal). Nuclear staining was performed with Hoechst 33342 (blue signal). Actin was imaged with phalloidin-binding (red signal). Inset shows a higher magnification of RAGE and HMGB1 stain.

\textbf{Figure S2} RAGE regulates chemotherapeutic-mediated ERK signaling.
(A) RAGE knockdown decreases phosphorylation of ERK (p-ERK) following treatment with anti-cancer drugs. The indicated Panc02 cells were treated with anti-cancer drugs (oxaliplatin, “OX”, 160 μg/ml; melphalan, “ME”, 320 μg/ml) for indicated time. Western blot analysis of protein levels is demonstrated here.

(B) RAGE knockdown decreases phosphorylation of ERK (p-ERK) following treatment with anti-cancer drugs when assessed by image analysis. The indicated Panc02 were treated with anti-cancer drugs (oxaliplatin, “OX”, 160 μg/ml; melphalan, “ME”, 320 μg/ml) for 30 min, then immunostained with pERK-specific antibodies (green signal). Nuclear staining was done with Hoechst 33342 (blue signal).

Figure S3 RAGE promotes tumor cell survival following chemotherapy.

Knockdown of RAGE in Panc02 pancreatic cancer cell lines treated with oxaliplatin and melphalan as indicated. Time and dose responses of cell viability were examined (n=3, * p < 0.05).

Figure S4 RAGE expression correlates with colony formation following treatment with chemotherapeutic agents.

The indicated Panc02 cells were treated with chemotherapeutic agents (oxaliplatin, “OX”, 160 μg/ml; melphalan, “ME”, 320 μg/ml; and gemcitabine, “GM”, 100 nM) for 24 h and were plated at a cell density of 2x10^3 cells per well in a 24 well cell culture plate. Colonies were visualized by crystal violet staining 3 weeks later.

Figure S5 RAGE over-expression increases autophagy and decreases apoptosis
following treatment with anti-cancer drugs.

Overexpression of RAGE in pancreatic cancer cells is indicated. Cells were then treated with chemotherapeutic agents (oxaliplatin, “OX”, 160 μg/ml; melphalan, “ME”, 320 μg/ml). Caspase-3 activity and LC3 punctae formation was examined at 24 h (n=3, * p < 0.05).

Figure S6 RAGE knockout increases apoptosis and decreases autophagy following treatment with anti-cancer drugs.

RAGE WT and KO fibroblasts were treated with anti-cancer drugs (oxaliplatin, “OX”, 160 μg/ml; melphalan, “ME”, 320 μg/ml) for 24 h. Western blot analysis of protein levels is presented.

Figure S7 RAGE knockdown increases phosphorylation of p53 at ser392 following treatment with UV irradiation.

Panc02 cells were treated with UV irradiation (5 min after 50 mJ/cm2) for 6 h. Western blot analysis of protein levels is presented with apparent phosphorylation of p53 at ser392.

Figure S8 An mTOR inhibitor reverses chemotherapy-induced autophagy in RAGE knockdown cells.

RAGE knockdown Panc02 cells were pretreated with an mTOR inhibitor (rapamycin, 1 μM) for 1 h and then treated with oxaliplatin (“OX”, 160 μg/ml) for 24 h. Western blot analysis of the protein levels is indicated.