**Supplementary Methods**

**Animal models**

All experimental use of animals abide by the Public Health Service Policy on Humane Care of Laboratory Animals, and was approved by the institutional animal care and use committee at Massachusetts General Hospital. All mice were bred and maintained in the Edwin L. Steele Laboratory gnotobiotic animal facility. C57BL/6, leptin-deficient (*ob/ob)* ( C57BL/6 background) and FVB mice were originally obtained from Jackson Laboratory (The Jackson Laboratory, Bar Harbor, Maine) and bred and maintained in our defined-flora colony. VEGFR-1 tyrosine kinase-null mice (*Flt1TK-/-*) of mixed C57BL/6 and SV129 strain background were originally developed at the University of Tokyo, Japan (1), and subsequently backcrossed to 99.9% C57BL/6 strain background (N10 equivalent) at Massachusetts General Hospital. Strain background was verified by the Jackson Laboratory’s Speed Congenic Development Service. Genotyping was performed using polymerase chain reaction (PCR) analysis. PlGF-null mice (*Plgf-/-*) mice, originally generated by Dr. Peter Carmeliet (Vesalius Cancer Research, Leuven, Belgium) (2), were obtained from Dr. Anne Croy (Queen’s University, Kingston, Canada). Age- and sex-matched animals were used for all experiments. Mice were maintained on a 12-h light-dark cycle in a temperature-controlled barrier facility with ad libitum access to food and acidified water, unless otherwise specified. At 6/7-weeks of age, all mice (with the exception of the *ob/ob* model, which remained on standard chow) switched from standard chow to either 10% (low-fat diet) or a 60% fat diet (high-fat diet) (D12450J and D12492, Research Diets, New Brunswick, NJ) for 10 weeks, as described previously (3). At the end of the experiment, animals were weighed and euthanized, and the inguinal, perigonadal, and perineal fat pads were excised and weighed.

**Tumor models**

C57BL/6 *Flt1TK-/-*, *Plgf-/-* or WT and FVB mice were used for tumor implantation studies after 10 weeks of diet, and the *ob/ob* model was used at 7 weeks of age. To induce pancreatic tumors, we grafted small (~1 mm in diameter) chunks derived from a PAN02 or AK4.4 pancreatic tumor source in the pancreata of obese and lean male mice. To induce breast tumors, we implanted 1x106 E0771 breast cancer cells in the mammary fat pad of lean and obese female mice. 3 weeks after implantation, pancreatic and breast tumors were removed, and tissue was assessed for immune cell infiltration, and gene and protein expression of inflammatory, metabolic and major signaling pathway markers (see below). Plasma was also collected and insulin, IGF-1, glucose and angiogenic/inflammatory markers were measured (see below). Metastatic burden was assessed by counting lung metastasis in the E0771 breast cancer model and evaluating abdominal wall invasion as well as mesentery metastasis in the PAN02 pancreatic model. For abdominal wall invasion, animals were scored from 0 to 3 based on the extent of invasion (0 = no invasion, 1 = less than 3 metastasis, 2 = less than 6 metastasis, 3 = more than 6 metastasis). For tumor implantation and collection, mice were anesthetized for 30 minutes using intramuscular injections of ketamine/xylazine (90mg/9mg per kg body weight). After surgery, Buprenorphine 0.1 mg/kg was awwwdministered every 12 hours for 72 hours. Criteria used for the decision to administer analgesics included ruffled fur, inability to self ambulate, hyper- or hypo-activity and the appearance of dehydration. If the aforementioned symptoms persisted, despite the use of analgesics for 3 days, the animal was removed from the study and euthanized. For tumor-bearing animals, body weight was monitored at least twice per week to ensure that the mice did not experience greater than 15% decrease in body weight. All animals were monitored by daily by the study staff, including weekends and holidays following procedures.

**Cell lines**

PAN02 cells (*SMAD4-m174*) (4) were obtained from ATCC. AK4.4 cells (*KrasG12D and p53+/-*) were kindly provided by Dr. Nabeel Bardeesy and were isolated from mice generating spontaneous pancreatic tumors (*Ptf1-Cre/LSL-KrasG12D/p53Lox/+*) (5). E0771 cells were obtained from Roswell Park Cancer Institute, Buffalo, NY. RAW 264.7 cells (mouse leukemic monocyte-macrophages obtained from ATCC) were grown in Dulbecco's modified Eagle's medium (Sigma, St. Louis, MO) supplemented with 5% (v/v) heat-inactivated fetal bovine serum (FBS; Sigma), 100 units/ml penicillin and streptomycin. HUVECs were acquired from the Center for Excellence in Vascular Biology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA and maintained in EGM medium (2% FBS, brain bovine extract, heparin, hEGF, and hydrocortisone) (Lonza). Cells were cultured at 37°C in a humidified atmosphere with 5% CO2.

Tumor cell authentication

PAN02 and AK4.4 tumor chunks, and E0771 cells were authenticated in 2013 by IDEXX laboratories. (PAN02: IDEXX RADIL Case # 22366-2013. The sample was confirmed to be of mouse origin and no mammalian interspecies contamination was detected. A genetic profile was generated for the sample by using a panel of microsatellite markers for genotyping. Without a sample representing the original cell line, it is not possible to make any interpretations in terms of authentication of the cell line. However, the sample is consistent with originating from a C57BL/6 mouse strain from which this cell line originated. A comparison profile is provided and the reference profile for the C57BL/6NCr mouse strain is identical to the cell line except for an allele size difference at marker 39. The genetic profile generated for this sample can be used for comparison of samples in the future. AK4.4: IDEXX RADIL Case # 27818-2014: Without a sample representing the original cell line, it is not possible to make any interpretations in terms of authentication of the cell line. However, the sample does have allele sizes consistent with the FVB mouse strain for 26 out of 27 markers tested (96%) and the cell line is consistent with originating from the FVB mouse strain. The genetic profile of the sample has an allele size difference at marker 5 compared to the FVB/NTac mouse strain. E0771: IDEXX RADIL Case # 14116-2013. The sample was confirmed to be of mouse origin and no mammalian interspecies contamination was detected. The genetic profile for this cell line contains extra alleles at 12 markers and different allele sizes at 5 markers. In addition, there are more than 2 alleles at 3 markers. The genetic profile for this cell line is not consistent with that of the C57BL/6 inbred mouse strain and is instead more consistent with having been derived from a mouse with a mixed/stock genetic background. Re-testing of this cell line after another 5-10 passages (IDEXX RADIL Case # 15518-2013) clarified that the genetic profile is intrinsic to this cell line but not likely cross-contaminated with another mouse cell line.)

**Analysis of adipose/tumor tissue and plasma**

Gene and protein expression were analyzed by real-time qPCR, PCR Array, Western blot, ELISA, and immunostaining. Immune cell profile was assessed by flow cytometry. Standard protocols were previously described (6-8).

Gene expression

Immediately following excision, tumor tissue was snap frozen and stored in liquid nitrogen until used. Total RNA was extracted and relative gene expression was determined using RT2 Profiler PCR Arrays system (Qiagen) on a Stratagene Mx3000P QPCR System. The pre-made pathway-focused arrays used (mouse genes, Qiagen) were “Inflammatory Cytokines and Receptors” (Cat. Number: PAMM011Z), “Common Cytokines” (Cat. Number: PAMM021Z), “T-cell and B-cell activation” (Cat. Number: PAMM053Z), and “Glucose Metabolism” (Cat. Number: PAMM006Z).

Western blot analysis

Each cell or tumor sample was homogenized directly in lysis buffer for protein extraction. 20ug of denatured protein per sample was loaded on 7%, 10% and 12% SDS-polyacrylamide gels. Membranes were blotted with antibodies against: MMP-9; cleaved caspase 3; phospho-ACCSer79 and ACC; phospho-AmpkβSer108 and Ampk; phospho-IRS-1Ser612; phospho-IGF-1RβTyr1135; phospho-IRY972; VEGFR-1; VEGFR-2; LC-3; GAPDH and ß-actin. Antibodies listed above were obtained from Cell Signaling (Beverly, MA), and diluted 1:100 with the exceptions of phospho-IRS-1 (1:200); phospho-IGF-1receptor β (1:200) and phospho-IR (1:500); VEGFR-1 (1:1000); VEGFR-2 (1:1000 Abcam), MMP-9 (1:500, EMD Millipore-Billerica, MA); GAPDH (1:2000, Ambion, NY) and ß-actin (1:5000, Sigma, MO).

ELISA/Multiplex array

Each cell/tumor sample was homogenized directly in lysis buffer for protein extraction. 2ug/ul of cell/tumor sample was used, data are expressed as pg/mg of tissue protein. Plasma was obtained from centrifugation of peripheral blood, and data is expressed as pg/ml of plasma. A pre-made inflammatory multiple cytokines protein array was used for both tumor homogenates and plasma (V-PLEX Proinflammatory Panel1 mouse kit, Cat. Number K15048D). IGF-1, VEGF-A, VEGF-B and PlGF were measured using mouse immunoassays (RD Systems, USCN for VEGF-B).

Immunohistochemistry/Immunofluorescence

Freshly excised pancreata and adipose tissue samples were fixed in 4% (vol/vol) paraformaldehyde overnight. 10μm sections were stained with hematoxylin and eosin (H&E) then examined for gross morphology. Insulin-producing cells were identified by staining with an anti-insulin primary antibody (R&D systems, Minneapolis, MN, USA) and a fluorescent secondary antibody. Islet size and pancreas surface area were quantified using a custom-written computer script. Pancreatic macrophages were identified by staining with a primary antibody against ER-MP23 (AbD Serotec, Raleigh, NC, USA) and a fluorescent secondary antibody. The number of macrophages (from at least 5 randomly selected 10× fields) was normalized by the pancreas surface area. Adipose tissue samples were evaluated for vessel density using a biotinylated rat anti-CD31 (Dianova) antibody, leukocytes using an anti-CD45 antibody (Serotec), and macrophages using F4/80 (Serotec) at 1:200 dilution. The expression of each marker (from at least 5 randomly selected 10× fields) was normalized by the total tissue area. Tissue sections stained with non-specific IgG, instead of specific primary antibodies, were used as negative controls. Images were taken using a brightfield microscope with camera attached. For analysis of tumor tissues, primary tumor tissues were snap frozen in liquid nitrogen, and later embedded in OCT compound. Staining was carried out on frozen sections (10-μm thick) using rabbit antibodies against Ki67 (Abcam), VEGFR-1, F4/80 (Serotec), CD31 (Millipore), GLUT-1 (Santa Cruz), CA-IX (Abcam), and IL-1β (Abcam) at 1:200 dilution, with the exception of ki67, IL-1β and F4/80 (1:100). Cy3-, Cy5- or FITC-conjugated secondary antibodies were used for the detection of signals by confocal microscopy. Cy5- streptavidin conjugated secondary antibody was used to detect lectin in tumor tissues. Slides were counterstained with DAPI for nuclear staining. Mosaic images of tumors were collected using an Olympus FV1000 confocal laser-scanning microscope. A 10x air objective acquired 1260-μm square tiles, and an automated stage scanned through the entire cross-section of each tumor tissue. The image tiles were stitched into a final mosaic image using Olympus software. Antigen expression was quantified by measuring the area occupied by the stain of interest normalized by the area of DAPI-stained nuclei, and analyzed using a custom algorithm in MATLAB.

Flow cytometry

Tumor-bearing mice were perfused via intracardiac injection of PBS and killed. Pancreatic and breast tumor tissues were harvested, minced, and digested at 37 °C for 1 h with DMEM containing collagenase type 1A (1.5 mg/mL), hyaluronidase (1.5 mg/mL), and DNase (2 mg/mL). The digestion mixtures were filtered through 70-μm cell strainers. Single-cell suspensions were incubated with rat anti-mouse CD16/CD32 mAb and then were stained, washed, and resuspended in cold buffer (1% BSA, 0.1% NaN3 in PBS). 7-Amino-actinomycin D (7AAD) reagent (eBioscience) was added to the stained tubes (5 μL per tube) just before performing the flow analysis. The doublet/aggregated events were gated out using forward scatter area (FSC-A) vs. forward scatter width (FSC-W) and side scatter area (SSC-A) vs. side scatter width (SSC-W). Flow cytometry data was acquired on an LSRII flow cytometer (Becton Dickinson) and analyzed with FACSDiva software. The appropriate fluorochrome-conjugated, isotype- matched control IgGs were used in all experiments. The following monoclonal anti-mouse antibodies were used: 7AAD (PerCP-Cy5.5, eBioscience), CD45 (PE-Cy7, Biolegend), CD45 (PerCP-Cy5.5eBioscience), CD4 (FITC, BD Bioscience), CD8 (PE, BD Bioscience), CD25 (APC-Cy7, BD Bioscience), NK (APC, BD Bioscience), F4/80 (PE-Cy7, Biolegend), CD11b (APC-Cy7, BD Bioscience), CD206 (FITC, Biolegend), Arginase-1 (FITC, R&D), and CD86 (PE, BD Biosciences).

Glucose homeostasis

Glucose (GTT) and insulin tolerance tests (ITT) were performed after 8 and 9 weeks on the diet, respectively. Male mice were fasted for 16 hours (5pm – 9am) for GTT, or 3 hours (9am – 12pm) for ITT. Glucose (0.75 mg/g body weight) or insulin (1U/kg body weight) was administered by intraperitoneal (i.p.) injection, and tail blood was sampled immediately before and at 15, 30, 60, 90, and 120 minutes after administration of glucose/insulin. Blood glucose levels were measured using a Precision Xtra glucose meter (Abbott Diagnostics, Bedford, MA, USA). Glucose tolerance was evaluated calculating the area under the curve (AUC) for each mouse according to the following equation:

 

Where Glc is glucose concentration, T is time, n is the time point number, and min(GlcTn,GlcTn+1) is the lower of two consecutive glucose concentrations (9). This equation adjusts for differences in fasting glucose levels so that the evaluation is based on the incremental area above the fasting baseline. For plasma insulin measurements, animals were fasted overnight before plasma was collected by tail bleed immediately before, and 30 minutes after intraperitoneal (i.p.) injection of 0.75 mg/g body weight glucose. Plasma samples were stored at –80°C until used. Plasma insulin concentration was determined using the Ultra Sensitive Mouse Insulin ELISA kit (Crystal Chem, Downers Grove, IL, USA).

**Metformin treatment**

Clinical standard doses of metformin range from 1000 to 2500 mg, usually given twice daily. In the present study, metformin was administered at 300 mg/kg to mice in drinking water. Using the Reagan-Shaw conversion method (10), we estimated that 300 mg/kg corresponds to 1459 mg for an average sized 60 kg adult human. Therefore, the selected dose is within the safe clinical therapeutic range. The amount given in the water was calculated based on the average daily water intake for a particular cage during a period of 2 weeks prior to treatment, and adjusted every three days based on water consumption and body weight of the animals. Drinking water was replaced every 3 days and at that time, metformin concentration in the water was adjusted for water consumption and mice BW.

**Human Samples**

The correlative study between body mass index and systemic levels of PlGF and VEGF-A in 73 pancreatic cancer patients was performed using data from a clinical study (11). The primary study cohort comprised 74 patients who underwent resection for primary pancreatic cancer at the Department of General, Visceral and Transplantation Surgery, the University of Heidelberg between November 2006 and April 2008. These patients had the histological diagnosis of pancreatic ductal adenocarcinoma and underwent R0 or R1 resection. Patients who received neoadjuvant chemoradiotherapy, with a history of a second malignancy, or with tumors that developed on the basis of intraductal papillary mucinous neoplasms or mucinous cystic neoplasms were excluded from the analysis. Body mass index was obtained for 73 patients and correlated with plasma levels of PlGF. For more details on the original study, refer to Rahbari *et al.* (11). The correlative study between visceral fat area and systemic levels of PlGF and VEGF-A in breast cancer patients was performed using data from a clinical study (NCT00546156) performed at Dana-Farber Cancer Institute and Massachusetts General Hospital (12). The primary study cohort comprised 99 patients (efficacy population). Enrollment required a pathological diagnosis of adenocarcinoma of the breast. Two cohorts of patients were eligible: patients with hormone-receptor (HR)+ tumors and patients with triple-negative (TN) tumors. Patients with HR+ tumors were eligible if they had high risk disease, defined as either having clinically positive axillary lymph nodes by pathological analysis, with a primary tumor ≥1.5 cm or no evidence of axillary lymph node involvement with a high grade tumor ≥1.5cm OR a low/intermediate grade tumor with a primary tumor ≥2.5cm. Patients could not have evidence of metastatic disease. Patients with bilateral cancers were eligible provided that at least one cancer met the eligibility requirements. Patients with TN breast cancer were required to have a tumor ≥1.5cm. Patients with a clinically negative axilla were required to have a sentinel lymph node biopsy performed either before starting preoperative therapy or at the time of definitive surgery. For patients with a clinically positive axilla, a needle aspiration or core biopsy was required prior to initiation of therapy. Patients with a positive sentinel node or needle biopsy at baseline were required to undergo a level I and II axillary lymph node dissection at the time of definitive surgery. From the patients above, measurements for PlGF, VEGF, and visceral adiopose tissue quantification (via computed tomography, see below) were obtained for 61 patients. For more details on the original clinical study, please refer to Tolaney *et al.* (12).

Abdominal visceral adipose tissue quantification

Abdominal visceral adipose tissue (VAT) was quantified based on computed tomography (CT) exams of the abdomen, which were acquired as part of the clinical work-up. Using a dedicated workstation (Syngo Volume Wizard; Siemens Medical Solutions), VAT was measured in a single CT slice at the level of the umbilicus (13, 14). The abdominal muscular wall separating VAT from subcutaneous adipose tissue was manually traced. Within the region of interest, any pixel with a CT number between -195 and -45 Hounsfield Units was defined as adipose tissue and VAT was calculated in cm2 (13, 15).

Statistical analysis

Statistical analysis was performed using GraphPad Prism Version 6.0f. Error bars indicate the standard error of the mean of data from replicate experiments. The significance of difference between samples within figures was confirmed using unpaired t-tests, one-way ANOVA, chi-square test or two-way ANOVA, depending on the experimental setting. Correlations between PlGF or VEGF-A and VAT or BMI were quantified and tested using Spearman's correlation coefficient and Spearman's test. A p value of less than 0.05 was considered significant.

**References (Supplementary Methods)**

1. Hiratsuka S, Minowa O, Kuno J, Noda T, Shibuya M. Flt-1 lacking the tyrosine kinase domain is sufficient for normal development and angiogenesis in mice. Proceedings of the National Academy of Sciences of the United States of America. 1998;95:9349-54.

2. Carmeliet P, Moons L, Luttun A, Vincenti V, Compernolle V, De Mol M, et al. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med. 2001;7:575-83.

3. Surwit RS, Feinglos MN, Rodin J, Sutherland A, Petro AE, Opara EC, et al. Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. Metabolism: clinical and experimental. 1995;44:645-51.

4. Wang Y, Zhang Y, Yang J, Ni X, Liu S, Li Z, et al. Genomic sequencing of key genes in mouse pancreatic cancer cells. Current molecular medicine. 2012;12:331-41.

5. Bardeesy N, Aguirre AJ, Chu GC, Cheng KH, Lopez LV, Hezel AF, et al. Both p16(Ink4a) and the p19(Arf)-p53 pathway constrain progression of pancreatic adenocarcinoma in the mouse. Proc Natl Acad Sci U S A. 2006;103:5947-52.

6. Kodack DP, Chung E, Yamashita H, Incio J, Duyverman AM, Song Y, et al. Combined targeting of HER2 and VEGFR2 for effective treatment of HER2-amplified breast cancer brain metastases. Proceedings of the National Academy of Sciences of the United States of America. 2012;109:E3119-27.

7. Chauhan VP, Martin JD, Liu H, Lacorre DA, Jain SR, Kozin SV, et al. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. Nature communications. 2013;4.

8. Huang Y, Yuan J, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proceedings of the National Academy of Sciences of the United States of America. 2012;109:17561-6.

9. Heikkinen S, Argmann CA, Champy MF, Auwerx J. Evaluation of glucose homeostasis. Curr Protoc Mol Biol. 2007;Chapter 29:Unit 29B 3.

10. Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. FASEB J. 2008;22:659-61.

11. Rahbari NN, Schmidt T, Falk CS, Hinz U, Herber M, Bork U, et al. Expression and prognostic value of circulating angiogenic cytokines in pancreatic cancer. BMC cancer. 2011;11:286.

12. Tolaney SM, Boucher Y, Duda DG, Martin JD, Seano G, Ancukiewicz M, et al. Role of vascular density and normalization in response to neoadjuvant bevacizumab and chemotherapy in breast cancer patients. Proceedings of the National Academy of Sciences of the United States of America. 2015;112:14325-30.

13. Irlbeck T, Massaro JM, Bamberg F, O'Donnell CJ, Hoffmann U, Fox CS. Association between single-slice measurements of visceral and abdominal subcutaneous adipose tissue with volumetric measurements: the Framingham Heart Study. Int J Obes (Lond). 2010;34:781-7.

14. Borkan GA, Gerzof SG, Robbins AH, Hults DE, Silbert CK, Silbert JE. Assessment of abdominal fat content by computed tomography. The American journal of clinical nutrition. 1982;36:172-7.

15. Maurovich-Horvat P, Massaro J, Fox CS, Moselewski F, O'Donnell CJ, Hoffmann U. Comparison of anthropometric, area- and volume-based assessment of abdominal subcutaneous and visceral adipose tissue volumes using multi-detector computed tomography. Int J Obes (Lond). 2007;31:500-6.