Supplemental Methods

Immunohistochemical analysis. Primary antibodies used for immunohistochemical analysis were rat monoclonal anti-mouse CD31 (BD Biosciences, Oxford, UK), rabbit polyclonal anti-human VEGF (Abcam plc, Cambridge, UK), rabbit anti-human phospho-Akt(Ser473) (Cell Signaling Technology, Inc.), rat monoclonal anti-mouse endomucin (Santa Cruz Biotechnology, Santa Cruz, CA), mouse monoclonal anti-human CD31 (Leica Biosystems, Newcastle Upon Tyne, UK) and mouse monoclonal anti-human LOX (Baker et al., 2011).

HUVEC wound closure assay. 3.5×10^6 HUVECs were seeded into 6-well plates and incubated in fully supplemented M199 media for 16 hours at 37^{o}C and 5% CO_2. Media was then exchanged for M199 supplemented with 3% FBS only, and the cells were incubated for 3 hours at 37^{o}C and 5% CO_2. Scratches were then made in the HUVECs using a sterile pipette tip, and the wells were washed three times with M199 medium. The media was replaced with M199 supplemented with 3% FBS, with added CRC CM (at 1:20 dilution), 50μg/ml bevacizumab (Roche, Welwyn Garden City, UK) or human IgG (Sigma-Aldrich), 100nM sunitinib (LC Laboratories, Woburn, MA) or vehicle (DMSO, Sigma-Aldrich) where indicated, before incubation at 37^{o}C for 8 hours. Pictures of each scratch were taken at 0 hours and 8 hours using an inverted light microscope, and percentage wound closure was calculated using ImageJ software (Abramoff et al., 2004).

Immunoblotting. Primary antibodies used were monoclonal mouse anti-human LOX (Baker et al., 2011), rabbit anti-human VEGF (Abcam plc), rabbit anti-human

phospho-Akt(Ser473) (Cell Signaling Technology, Inc.), rabbit anti-human Akt (Cell Signaling Technology, Inc.), mouse anti-human β actin (Abcam plc), rabbit anti-human phospho-PDGFRβ(Tyr751) (Cell Signaling Technology, Inc.), rabbit anti-human PDGFRβ (Cell Signaling Technology, Inc.), rabbit anti-human phospho-VEGFR2(Tyr1175) (Cell Signaling Technology, Inc.), rabbit anti-human VEGFR2 (Cell Signaling Technology, Inc.), rabbit anti-human phospho-PLC-γ(Tyr783) (Cell Signaling Technology, Inc.) and rabbit anti-human PLC-γ (Cell Signaling Technology, Inc.). Cells were treated with recombinant human LOX protein (Origene, Rockville, MD) at 150ng/ml for 16 hours prior to lysis and immunoblot analysis. Treatment with rabbit polyclonal LOX-targeting antibody was as previously described (Baker et al., 2011). A 20mM stock solution of the Akt inhibitor MK-2206 (Chemietek, Indianapolis, IN) was prepared in DMSO, then added to cell media at the indicated concentrations. Cells were then incubated at 37^{o}C for 16 hours before analysis. Analysis of PDGFRβ phosphorylation involved serum starving cells for 5 hours, pre-incubating with increasing concentrations of PDGFRβ inhibitor JNJ-10198409 (Sigma-Aldrich) for 1 hour at 37^{o}C followed by stimulation with 25ng/ml PDGF-BB (PeproTech, London, UK) for 2 minutes. Cells were then lysed and analyzed as previously described (Baker et al., 2011).

Quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR)

The primers sequences are listed below:

Human VEGF, Forward (Zhang et al., 2003): 5'-

AACCATGAACTTTCTGCTGTCTTG-3'

Human VEGF, Reverse (Zhang et al., 2003): 5'-

TTCACCACTTCGTGATGATTCTG-3'

Human LOX, Forward: 5'-CGTCCACGTACGTGCAGAAG-3'

Human LOX, Reverse: 5'-CCTGTATGCTGTACTGGCCAGAC-3'

Human β actin, Forward: 5'-GAGGCCCAGAGCAAGAGAGG-3'

Human β actin, Reverse: 5'-TACATGGCTGGGGTGTTGAA-3'

Murine VEGF, Forward (Liu et al., 2011): 5'-GTTCACTGTGAGCCTTGTTCAG-3'

Murine VEGF, Reverse (Liu et al., 2011): 5'-GTCACATCTGCAAGTACGTTCG-3'

Murine LOX, Forward: 5'-CAGAGGAGAGTGGCTGAAGG-3'

Murine LOX, Reverse: 5'-CCAGGACTCAATCCCTGTGT-3'

Murine β actin, Forward: 5'-GTGACGTTGACATCCGTAAAGA-3'

Murine β actin, Reverse: 5'-GCCGGACTCATCGTACTCC-3'

***In vivo* sponge assay.** Sponges were and injected *in situ* three times weekly with 100µl CM collected from SW480 or SW620 CRC cells. Concentrated serum-free phenol-red free media was injected as a negative control and murine VEGF/FGF (10ng/ml each; R&D Systems/Peprotech) was injected as a positive control. Treatment with human IgG or bevacizumab involved bi-weekly intraperitoneal injection at 5mg/kg. Treatment with sunitinib (40mg/kg) or vehicle (300mM sodium chloride, 20µM carboxylmethylchloride, 0.4% Tween 80, 0.9% benzyl alcohol [All obtained from Sigma-Aldrich]) was by daily oral gavage. The technician who treated the mice was blinded to the specificity of the treatments. Balb/c nude mice were used for the groups treated with human IgG or bevacizumab, C57BL/6 mice were used for all other treatment groups. After 3 weeks, sponges were excised and fixed in 4% PFA in PBS for 24 hours before processing.

Supplemental Methods References

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