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Update on Antiangiogenic Therapy for Metastatic Colorectal Cancer

Edited by Cathy Eng, M.D. and J. Randolph Hecht, M.D.

Cancer of the colon and rectum caused an estimated 49,960 deaths in the U.S. in 2008[1]. The addition of biologic agents and targeted therapies to cytotoxic chemotherapy regimens, combined with better surgical techniques and advanced imaging, has led to improved outcomes among patients with metastatic colorectal cancer (mCRC) over the past decade. However, not all patients respond to these therapies and many develop resistance and, ultimately, disease progression. There is therefore an urgent need to better select patients who can benefit from these treatments.

Angiogenesis plays an important role in the development, invasion and metastasis of colorectal and other solid tumors[2]. In colorectal cancer, increased angiogenesis in the primary tumor is associated with poor prognosis, relapse, and metastasis[3]. The predominant mediator of tumor angiogenesis is vascular endothelial growth factor (VEGF), an endogenous cytokine that stimulates endothelial cells to proliferate and migrate from pre-existing vessels toward VEGF-expressing tumors cells to form new vascular tubes. VEGF production is driven primarily by hypoxia in the tumor microenvironment, but may also be stimulated independently by acquired genetic mutations[2]. Other growth factors implicated in angiogenesis in CRC include fibroblast growth factor (FGF), transforming growth factor-α (TGF-α), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF)[3]. Additionally, colorectal tumors underexpress the endogenous angiogenesis inhibitor thrombospondin-1 (TSP-1); tumor deficiency of this protein correlates with increased microvessel density, poor prognosis, and hepatic recurrence[3].

The liver is the preferred metastasis site for CRC, at least partly due its favorable microenvironment for tumor development and an abundance of certain angiogenic growth factors that, while necessary for tissue regeneration following injury or resection, facilitate tumor angiogenesis in the setting of advanced CRC[3]. Experimental studies indicate that angiogenesis in liver metastases is initiated when tumors co-opt sinusoidal endothelial cells lining the periphery of the metastatic lesion. Vessels formed by these cells are typically convoluted, fenestrated, and lack a basement membrane[3].

Antiangiogenic agents specifically designed to target the VEGF pathway include monoclonal antibodies that bind and sequester circulating angiogenic proteins, and small molecule, orally administered multi-targeted tyrosine kinase inhibitors (TKIs) that disrupt intracellular angiogenic signaling by binding competitively to the ATP binding sites on VEGF receptors (VEGFR-1, -2, and -3) and related growth factors, notably platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-Kit). The epidermal growth factor receptor (EGFR) has also been correlated with increased tumor pathogenesis and angiogenesis resulting from deregulation of numerous cell functions[3, 4]. Cetuximab (Erbitux®), a chimeric monoclonal antibody against EGFR, directly inhibits tumor growth and may also exert antiangiogenic effects by blocking ligand-induced phosphorylation of EGFR on tumor vessel endothelial cells, thereby inhibiting their proliferation[5]. mCRC patients are now selected for treatment with EGFR inhibitors based on *KRAS* mutation status—presence of the mutated form of this gene results in the constitutive activation of the EGFR extracellular ligand, and thereby renders anti-EGFR therapy ineffective[6].

From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this issue of *Targeting Tumor Angiogenesis: Update on Antiangiogenic Therapy for Metastatic Colorectal Cancer.* Two preeminent experts, Dr. Cathy Eng and Dr. J. Randolph Hecht, discuss the latest evidence on antiangiogenic treatments for mCRC and what the future holds for new therapeutic targets under investigation.

– *William W. Li, M.D., President, The Angiogenesis Foundation*

Clinical Evidence for Antiangiogenic Therapy

Anti-VEGF Monoclonal Antibodies

Bevacizumab (Avastin®; BV), a humanized monoclonal antibody against VEGF-A, was first approved for mCRC in combination with IFL chemotherapy (irinotecan/bolus 5-FU/leucovorin) after a randomized phase 3 trial showed that this combination significantly improved progression free survival (PFS) and overall survival (OS) versus chemotherapy alone in previously untreated patients[7]. Following on this data, the ECOG E3200 trial established the efficacy of BV 10 mg/kg plus FOLFOX (5-FU/leucovorin/oxaliplatin) in the second-line mCRC setting[8]. A more recent randomized phase 3 trial (NO16966) assessed the addition of BV to the more modern FOLFOX4 or XELOX (capecitabine and oxaliplatin) regimens in front-line mCRC[9]. The primary pooled analysis from this trial (BV vs. placebo-containing arms) showed only a modest PFS advantage with the addition of BV (9.4 mo. vs. 8.0 mo., P=0.0023), and no significant improvement in OS (21.3 mo. vs. 19.9 mo)[9]. A subset analysis did show a significant PFS improvement relative to placebo with BV plus XELOX (P=0.0026). In a retrospective exploratory analysis, however, PFS was significantly improved in both BV arms for patients who remained on therapy, suggesting a possible advantage of continuing BV until progression[9].

Whether mCRC patients may derive some clinical benefit from continuing on a BV-containing regimen in the context of disease progression is controversial and, as of yet, unproven. In a large non-randomized, non-prospective observational study (BRiTE), continuation of BV beyond first progression significantly improved median OS compared with systemic therapy without BV (31.8 mo. vs. 19.9 mo.)[10]. Several prospective randomized trials are now looking at this question. These include the phase 3 Intergroup Bevacizumab Continuation Trial/SWOG 0600 trial of irinotecan-based chemotherapy (CT) with continuation of BV or weekly cetuximab; the phase 3 AIO 0504/GMT trial comparing CT with or without BV in 572 second-line mCRC patients who progressed on a first-line BV-containing regimen[11]; and SPIRITT, a randomized phase 2 trial comparing FOLFIRI (irinotecan/infusional 5-FU/leucovorin) plus BV to FOLFIRI plus the anti-EGFR antibody panitumumab (Vectibix®) in 210 second-line mCRC patients with wild-type (non-mutated) *KRAS*[12].

Anti-VEGF-EGFR Combination Therapy

Experimental evidence has suggested that combined blockade of the VEGF and EGFR pathways may have synergistic anti-tumor effects[13]. In the clinical setting, a phase 2 study (BOND-2) showed some initial promise in the form of prolonged time-to-progression with the addition of BV to cetuximab and irinotecan in a small number of irinotecan-refractory mCRC patients[14]. These results, however, were starkly contradicted by two much larger randomized phase 3 studies—PACCE and CAIRO2. In PACCE, investigators added panitumumab 6 mg/kg to BV 5 mg/kg plus either oxaliplatin or irinotecan in 1,053 previously untreated mCRC patients[15]. Surprisingly, this combination worsened both PFS and OS. CAIRO2, which evaluated the combination of BV 7.5 mg/kg plus capecitabine and oxaliplatin with or without cetuximab in 755 patients with previously untreated mCRC, produced similar results[16]. Compared with BV plus CT, the cetuximab-containing arms had equivalent response rates (P=0.49), significantly worse PFS (9.4 mo. for CT-BV-cetuximab vs. 10.7 mo. for CT-BV; P=0.01), and reduced median OS (19.4 vs. 20.3 mo., P=0.16)[16]. Patients in the anti-VEGF/EGFR combination arms in both studies also had an increased incidence grade of 3/4 toxicities. Also of note, when stratified by *KRAS* mutation status, patients with wild-type tumors did not fare any better receiving panitumumab or cetuximab combined with BV.

Two ongoing Phase 3 trials in mCRC with cetuximab-BV combination arms—S0600 in second-line mCRC and the North American Intergroup trial C80405 in untreated mCRC—are responding differently to this new data. Investigators on S0600 will be re-initiating accrual without the original combination cetuximab-BV treatment arms; C80405, in contrast, is retaining its anti-VEGF/EGFR combination arms, but is requiring that all patients have *KRAS* wild-type tumors.

Tyrosine Kinase Inhibitors

Thus far, VEGFR TKIs have produced limited results for mCRC, but a number of phase 3 trials are underway. Sunitinib (Sutent®), approved for the treatment of renal and gastrointestinal stromal tumors, is being evaluated in two first-line trials: a multinational, randomized phase 3 trial with or without FOLFIRI, as well as a randomized phase 2 trial of sunitinib plus FOLFOX vs. BV plus FOLFOX. Cediranib (AZD2171, Recentin®) has shown initial promise for the treatment of glioblastoma[17], and is now the investigational agent in two randomized phase 3 trials in front-line mCRC: HORIZON II (cediranib or placebo plus either FOLFOX or XELOX); and HORIZON III (cediranib plus FOLFOX compared with BV plus FOLFOX). Sorafenib (Nexavar®), approved for liver and renal cancers, is in phase 2 development for mCRC. Another small molecule agent, axitinib, is being combined with chemotherapy (FOLFOX and FOLFIRI) and BV, and also compared against CT-BV in two separate phase 2 trials in mCRC.

Side Effects of Antiangiogenic Therapy in mCRC

Hypertension is the primary side effect of all VEGF inhibitors and can usually be effectively managed with anti-hypertensive medications when treated early and aggressively. BV therapy has been commonly associated with thromboembolic events, and infrequently with episodes of GI perforation, reversible posterior leukoencephalopathy, hemorrhage, nasal septum perforation, and delayed wound healing, which is of particular concern in the neoadjuvant mCRC setting. Results from a non-randomized phase 2 study in 56 mCRC patients showed that treatment with BV 5 mg/kg plus XELOX prior to resection of liver metastases with curative intent did not affect wound healing or liver regeneration when BV was discontinued 5 weeks prior to surgery and reinstated 5 weeks post-surgery[18]. Current recommendations suggest discontinuing BV at least 4-6 weeks prior to liver resection[19]. Toxicities from multi-targeted VEGFR TKIs are typically more diverse than monoclonal antibodies, possibly due to the relative non-specificity of these agents, and may include diarrhea, fatigue, nausea, hypertension, stomatitis, mucosal inflammation, hand-foot skin reaction, and hair and nail changes[20]. Cardiac events, including a variety of ECG changes and reduced LVEF have been reported with both sunitinib and sorafenib[21]. Patients on sunitinib may also require monitoring for hypothyroidism[22].

Future Directions

Despite the multiple therapeutic advances in the treatment of mCRC, only 10% of patients with surgically unresectable disease are expected to be alive at 5 years. Therefore, the majority of mCRC patients continue to receive therapy with only palliative intent. The continued pursuit of novel agents and the validation of predictive therapeutic biomarkers is clearly needed. The *KRAS* mutation is the first universally accepted predictive marker in mCRC, but applies only to EGFR inhibitors. While preclinical research has shown that VEGF levels and VEGFR-2 expression may be both predictive and prognostic, there is no consistent data correlating VEGF/VEGFR-2 expression with outcome or efficacy. Small studies in a number of tumor types have indicated a correlation between the development of hypertension and clinical response with VEGF inhibitors, however prospective trials are needed to determine the significance of this data[23, 24]. In the CONFIRM-1 trial involving vatalanib (PTK787/ZK), elevated levels of lactate dehydrogenase (LDH), a marker of hypoxia and increased angiogenesis, was predictive of response[25]. Other potential biomarkers include circulating endothelial progenitor cells (CEPs)—CEP levels decrease during anti-VEGF therapy, which may reflect shedding of non-viable tumor endothelial cells; angiopoietins—ligands that bind competitively to Tie-2 receptor, the activation of which promotes angiogenesis and vascular maturation; and tumor endothelial markers (TEMs), which are overexpressed in colorectal tumor cells[26].

Numerous antiangiogenic therapies are in development. Phase 1 and 2 clinical trials include agents that neutralize hepatocyte growth factor (HGF); an agent that blocks both VEGF and FGF-mediated signaling; and a thrombospondin-1 (TSP-1) mimetic. TSP is an endogenous inhibitor of angiogenesis, and loss of TSP-1 via the PI3K signaling pathway is one of the first steps in angiogenesis[26]. Other agents of interest in mCRC are selective angiopoietin antagonists that inhibit Tie-2-dependent stimulation of endothelial cells. One agent, AMG 386, a selective angiopoietin-1, -2-neutralizing peptibody, is being evaluated in a randomized, placebo-controlled phase 2 trial in second-line mCRC. Despite the majority of mCRC patients being non-curative, the number of promising therapies in clinical trials should be cause for optimism.

Guest editors:

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Abbreviated References:
1. CAFF 2008 2. Kerbel RS (2008) 3. Stoeltzing O (2003) 4. Italiano A (2005) 5. Amin DN (2008) 6. Jimeno A (2009) 7. Hurwitz H (2004) 8. Giantonio BJ (2007) 9. Saltz LB (2008) 10. Grothey A (2008) 11. Arnold D (2008) 12. Hecht JR (2008) 13. Tonra JR (2006) 14. Saltz LB (2007) 15. Hecht JR (2008) 16. Tol J (2009) 17. Batchelor T (2007) 18. Gruenberger B (2008) 19. Bilchick AJ (2008) 20. Robert C (2005) 21. Schmidinger M (2008) 22. Sutent PI (2009) 23. Scartozzi M (2009) 24. Bono P (2009) 25. Hecht JR (2007) 26. Folkman J (2007)

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This CME activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the Joint Sponsorship of the Boston University School of Medicine and the Angiogenesis Foundation. Boston University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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RELEASE AND EXPIRATION
Release date is March 31, 2009. Expiration is March 31, 2010.

INTENDED AUDIENCE
Practicing oncologists in the U.S.

EDUCATIONAL OBJECTIVES
At the conclusion of this educational activity, clinicians will be able to:
- Describe angiogenesis pathways and molecular targets in metastatic colorectal cancer.
- Describe the rationale for antiangiogenic therapy for metastatic colorectal cancer.
- Review the clinical data regarding the safety and efficacy of antiangiogenic agents for metastatic colorectal cancer.

METHOD OF PARTICIPATION
Review the illustration and article, then visit www.angio.org and click on CME Publications. There you can register for this CME activity, take the post-test, and access instructions for obtaining CME credits.

ACKNOWLEDGEMENT OF SUPPORT
This activity is supported by educational grants from AstraZeneca, Genentech and Pfizer.

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Cathy Eng, M.D., The University of Texas M.D. Anderson Cancer Center, receives grant/research support from Genentech and Pfizer.

J. Randolph Hecht, M.D., David Geffen School of Medicine at UCLA, receives honoraria from Genentech, Imclone and Roche.

Course Director: Vickie R. Driver, DPM, M.S., FACFAS, Boston University School of Medicine, receives grant/research support from Johnson & Johnson, KCI, sanofi-aventis, and Baxter; is on the speaker's bureau for Johnson & Johnson, KCI, and sanofi-aventis; and is consultant for sanofi-aventis and Baxter.

Executive Editor: William W. Li, M.D., the Angiogenesis Foundation, has nothing to disclose with regard to commercial interests.

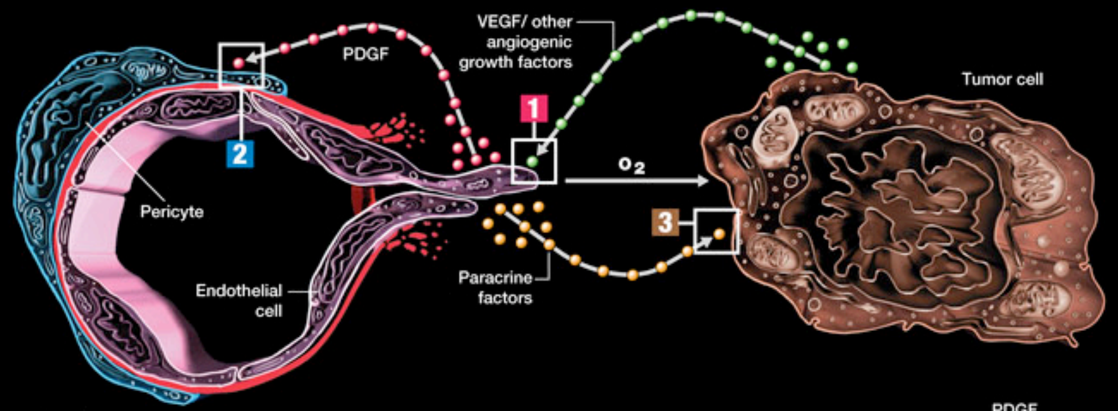
Program Manager: Ilana Hardesty, Boston University School of Medicine, Department of Continuing Medical Education, has nothing to disclose with regard to commercial interests.

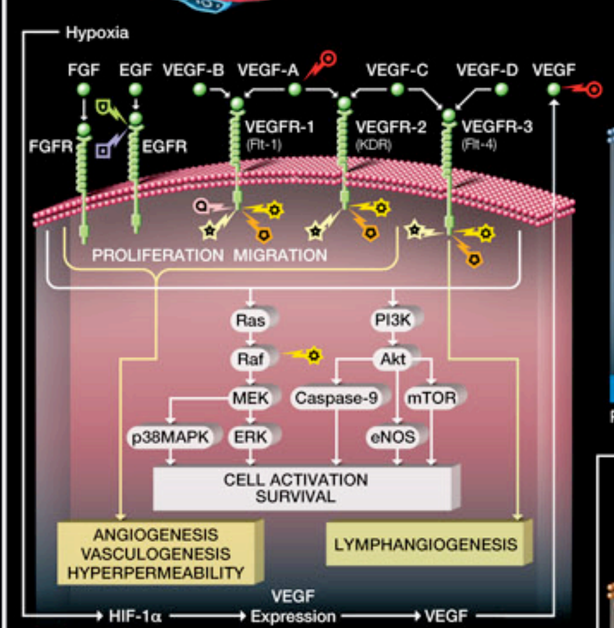
Medical Writer: Roderick A. Smith, M.S., the Angiogenesis Foundation, has nothing to disclose with regard to commercial interests.

DISCUSSION OF UNLABELLED USE
This CME activity contains discussion of published and/or investigational use of: AMG 386, axitinib, bevacizumab (Avastin®), cediranib (AZD2171; Recentin®), cetuximab (Erbitux®), panitumumab (Vectibix®) sorafenib (Nexavar®), sunitinib (Sutent®), vatalanib (PTK787/ZK).

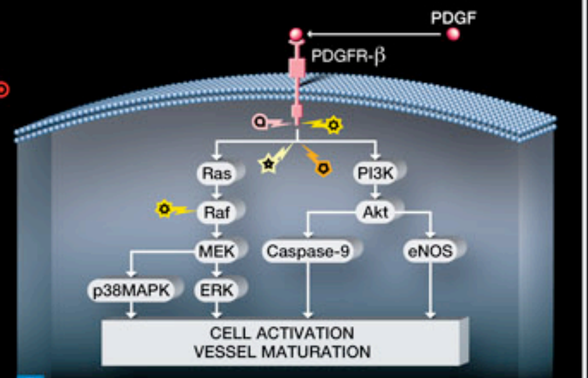
Targeting Cells and Pathways in Metastatic Colorectal Cancer

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells, which in turn, release growth factors that sustain angiogenesis. Antiangiogenic agents target key pathways in proliferating endothelial cells, pericytes, and tumor cells.

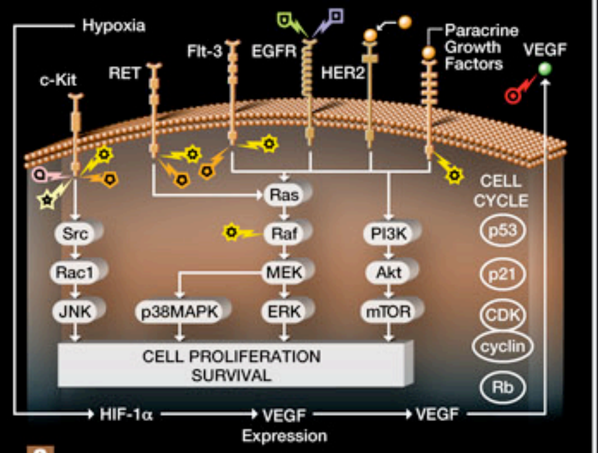




1 ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGFR-1, VEGFR-2, VEGFR-3, activating signal transduction to promote angiogenesis,vasculogenesis, and lymphangiogenesis.



2 PERICYTE Platelet-derived growth factor (PDGF) and its receptor PDGFR-β mediate vessel maturation.



3 TUMOR CELL Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

Targeted Agents (Targets shown in diagram above)

- **AMG 386**
- **Axitinib** (AG-013736)
- **Bevacizumab** (Avastin®)
- **Cediranib** (AZD2171, Recentin®)
- **Cetuximab** (Erbitux®)
- **Panitumumab** (Vectibix®)
- **Sorafenib** (Nexavar®)
- **Sunitinib** (Sutent®)

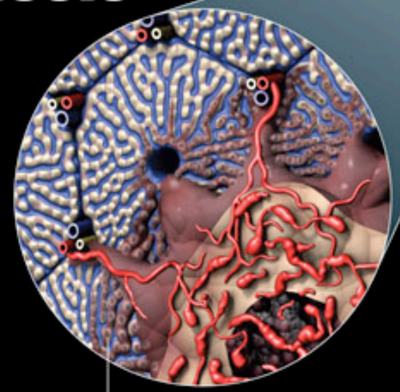
Targeting Tumor Angiogenesis

1 Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to acquired gene mutations and hypoxia.

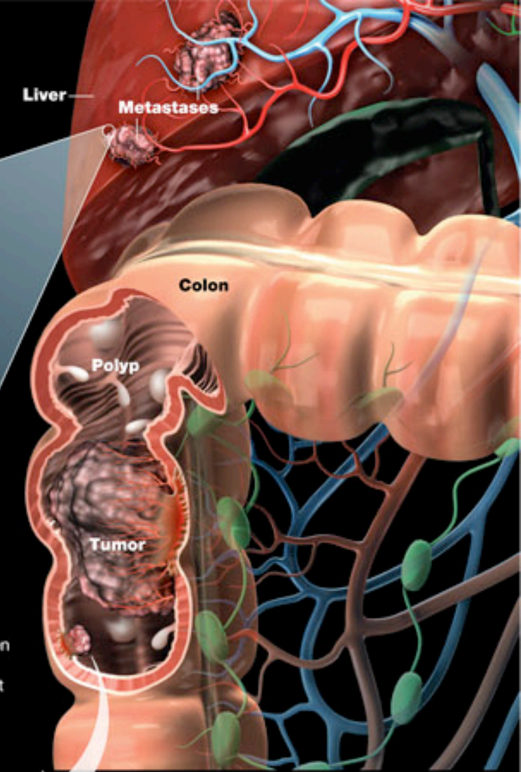
2 Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation.

3 Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αβ integrins.

4 Tumor blood vessels are characteristically tortuous, saccular, and leaky; blood flow is uneven and chaotic, with areas of tumor necrosis, hypoxia, and acidosis.



Angiogenesis in CRC liver metastases is initiated when a tumor co-opts sinusoidal endothelial cells lining the periphery of the lesion. The liver contributes abundant proangiogenic factors to the metastatic lesion.



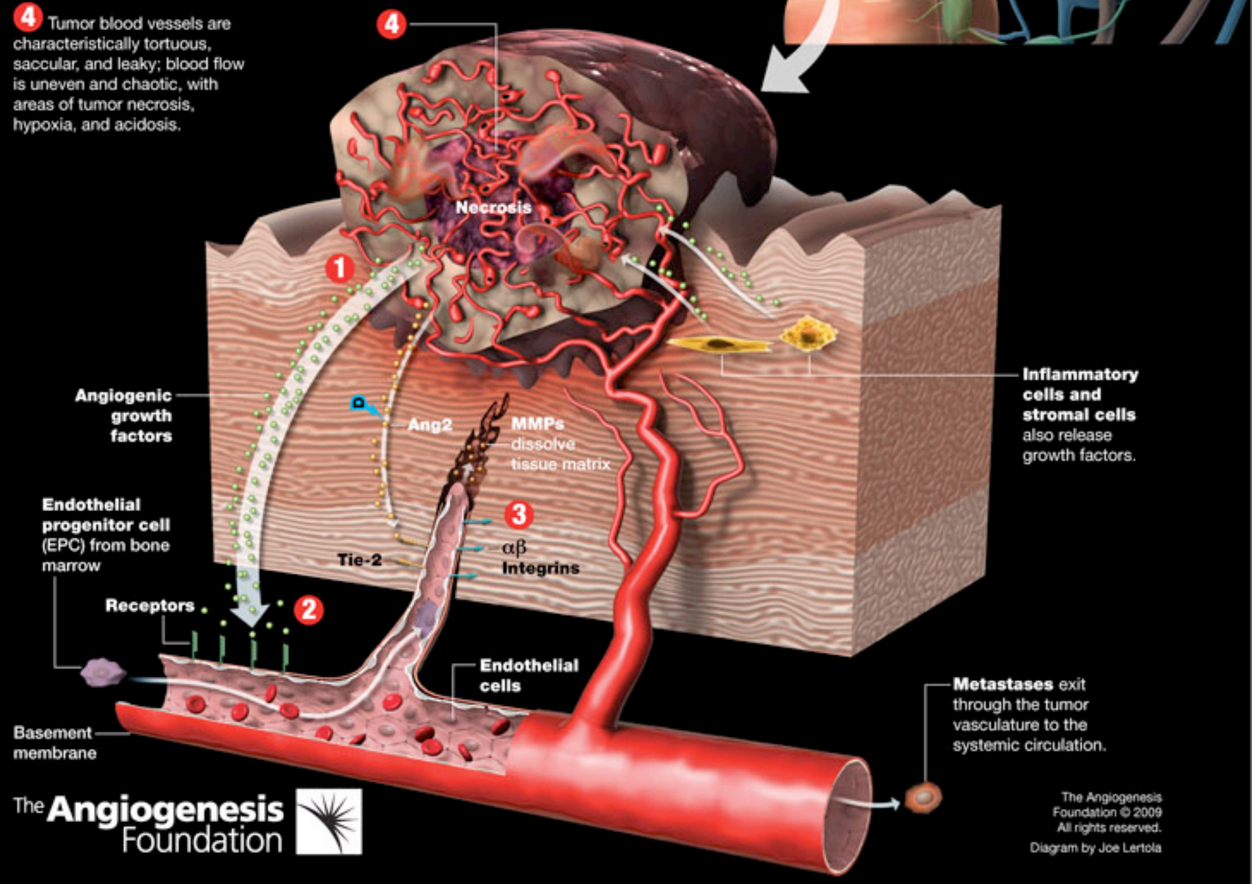


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Diagram by Joe Lertola