

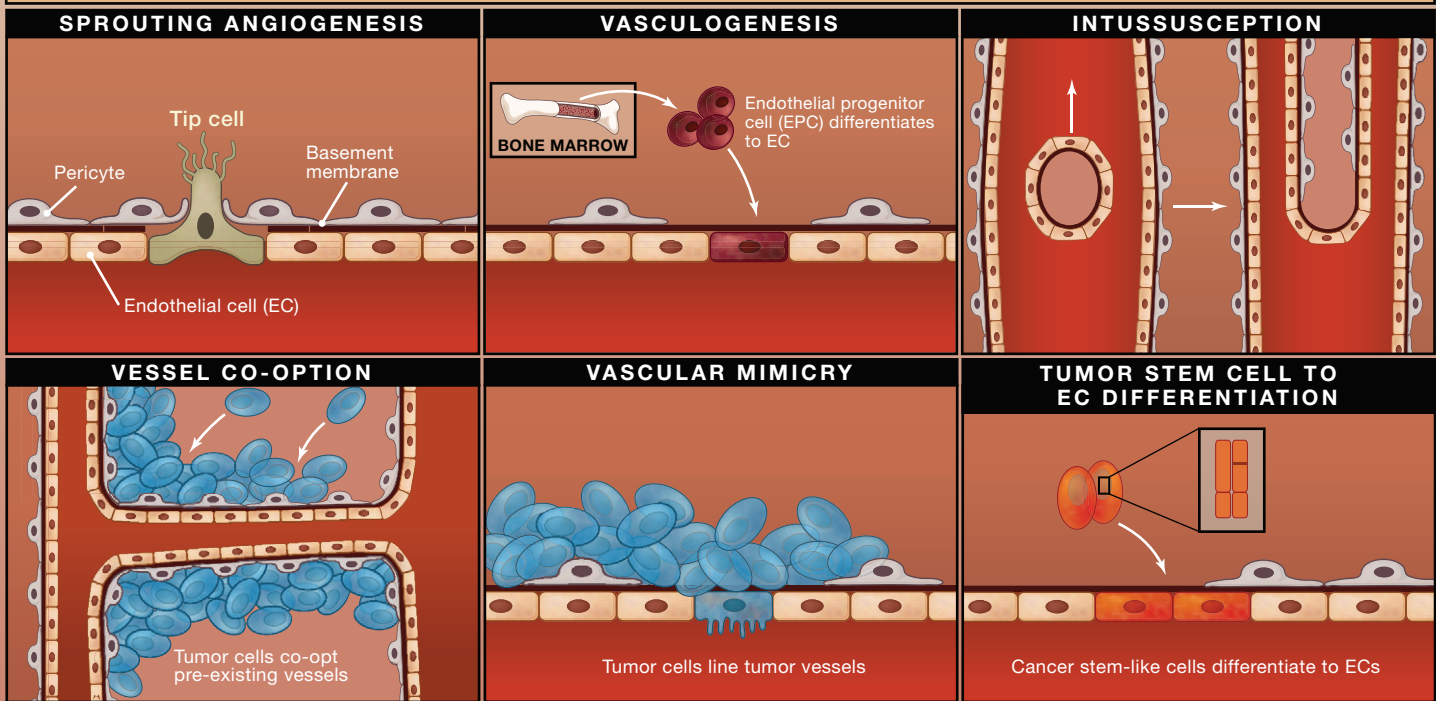
SnapShot: Tumor Angiogenesis

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How do tumors recruit blood vessels?



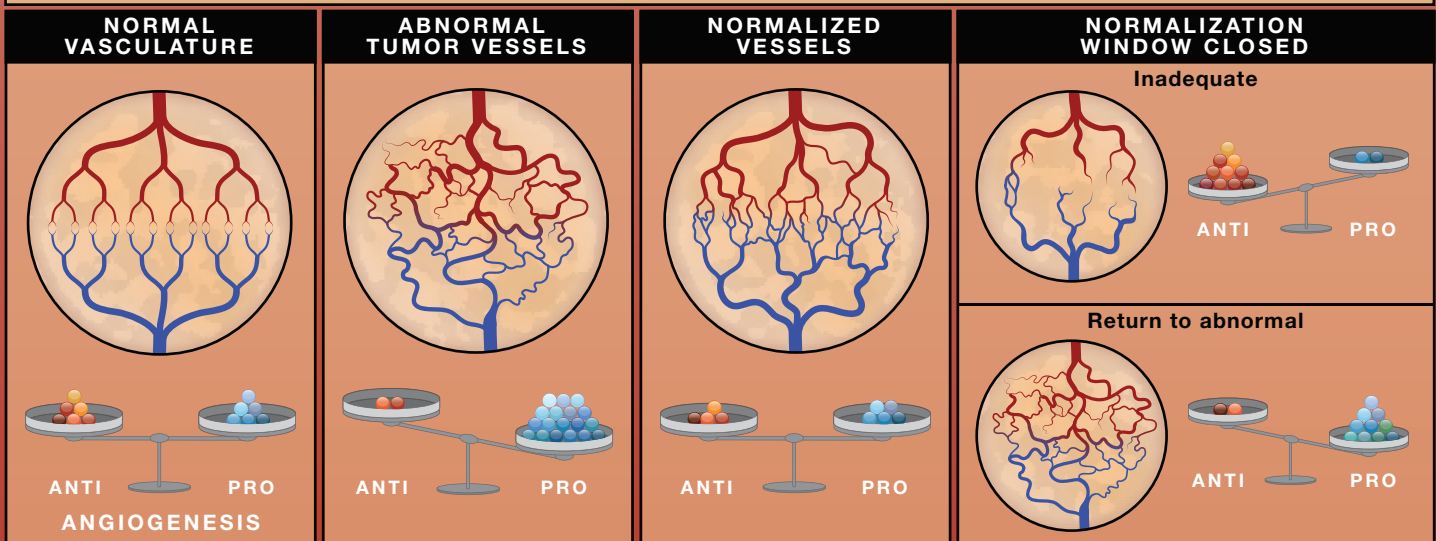
Anti-VEGF drugs (2012)

Bevacizumab	Metastatic colorectal cancer, metastatic nonsquamous non-small cell lung cancer, metastatic breast cancer, recurrent glioblastoma, metastatic renal cell carcinoma
Sunitinib	Metastatic renal cell carcinoma, gastrointestinal stromal tumors, pancreatic neuroendocrine tumors
Sorafenib	Metastatic renal cell carcinoma, unresectable hepatocellular carcinoma
Pazopanib	Metastatic renal cell carcinoma, advanced sarcoma
Vandetanib	Advanced medullary thyroid cancer
Axitinib	Advanced renal cell carcinoma
Regorafenib	Metastatic colorectal cancer (approval pending)
Aflibercept	Metastatic colorectal cancer (approval pending)

Anti-angiopoietin/Tie2 pathway agents (in clinical trials)

AMG 386	Ovarian, breast, gastric, hepatocellular carcinoma, renal cell carcinoma, endometrial, colorectal carcinoma, glioblastoma
CVX-060	Renal cell carcinoma
CVX-241	Ovarian, primary peritoneal
MEDI-3617	Advanced solid tumors
REGN910	Advanced solid tumors
AMG-780	Advanced solid tumors
CEP-1198	Advanced solid tumors
ARRY-614	Myelodysplastic syndromes
MGCD265	Advanced malignancies, non-small cell lung carcinoma
Regorafenib	Gastrointestinal, renal cell carcinoma

How does anti-angiogenic therapy work?



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How Do Tumors Recruit Blood Vessels?

Blood vessels are indispensable for tumor growth and metastasis. Hence, tumors exploit multiple avenues to recruit blood vessels. Angiogenesis—the sprouting of new blood vessels from the existing vasculature—is the most widely investigated mode of new vessel formation in tumors. There are five other mechanisms of new vessel recruitment (top panels; adapted from Carmeliet and Jain, 2011). However, their relevance in cancer is still being debated, and their molecular mechanisms are not well understood. Vasculogenesis involves vessel formation by endothelial progenitor cells (EPCs), which are recruited from the bone marrow and/or are resident in vascular walls. Intussusception is the splitting of pre-existing vessels to give rise to daughter vessels. Vessel co-option occurs when cancer cells grow around and co-opt the existing vasculature. Vascular mimicry is a process in which cancer cells get incorporated into the blood vessel wall. Tumor stem cell to EC differentiation occurs when cancer stem-like cells differentiate into endothelial cells (ECs). For historical reasons and, now, for convenience, the term “angiogenesis” is used to describe all of these methods of blood vessel recruitment by tumors.

What Are the Approved and Emerging Anti-angiogenic Drugs?

Anti-VEGF Drugs

Eight drugs that target the vascular endothelial growth factor (VEGF) pathway have already been approved or are pending approval for treatment of a variety of solid tumors (left table; updated from Carmeliet and Jain, 2011), and three others (not shown) have been approved for age-related wet macular degeneration that can lead to blindness. Among these, the anti-VEGF antibody bevacizumab (Avastin) is the most widely prescribed drug and has shown benefit in patients only when combined with chemotherapy or immunotherapy. An exception was its conditional approval for use as a monotherapy for recurrent glioblastoma, but confirmatory data from randomized phase III trials in these patients are pending. Although the US FDA has withdrawn approval of bevacizumab for metastatic breast cancer in the US, this drug is still given to these patients in Europe, except for in the United Kingdom. All other approved anti-VEGF agents are multitargeted receptor tyrosine kinase inhibitors and may have off-target effects.

Anti-angiopoietin/Tie2 Pathway Agents

Similar to all targeted therapies, tumors develop resistance to anti-VEGF drugs. Therefore, considerable research and clinical effort is now directed toward finding new targets beyond VEGF (right table; adapted from Cascone and Heymach, 2012). One such target is the Angiopoietin/Tie2 pathway, which is involved in vessel stability. Eight agents that target this pathway (specifically or in combination with the VEGF pathway) are in clinical trials for multiple solid tumors.

How Does Anti-angiogenic Therapy Work?

Anti-angiogenic therapy was originally developed to “starve” primary and metastatic tumors by blocking blood vessel recruitment. However, this concept has yet to be clinically validated because bevacizumab alone has failed to show survival benefits in randomized phase III trials to date. In fact, in several trials, bevacizumab monotherapy was discontinued for lack of efficacy. In contrast, bevacizumab added to chemotherapy or immunotherapy improved outcome in multiple phase III trials. Here, we offer one potential mechanism of this benefit (bottom; adapted from Jain, 2005).

In a normal tissue, the signals downstream of the pro-angiogenic molecules, such as VEGF and Ang2, are exquisitely counterbalanced by those from anti-angiogenic molecules such as sVEGFR1, thrombospondins, and semaphorins. Thus, the blood vessels exhibit normal structure and function (panel 1). In contrast, due to genetic and epigenetic changes, the balance is tipped in favor of new vessel formation in tumors. As a result, tumor vessels are highly abnormal both structurally and functionally (panel 2). This creates a hostile microenvironment in tumors—characterized by hypoxia, low pH, and elevated fluid pressure—which fuels tumor progression and treatment resistance via genetic instability, angiogenesis, immune suppression, inflammation, resistance to cell death, etc. If VEGF is neutralized using bevacizumab (or another anti-VEGF drug), this can cause pruning of some abnormal vessels and remodeling of the remaining vessel, resulting in a “normalized vasculature” (panel 3). In turn, this can reduce tumor hypoxia and fluid pressure that will improve the outcome of chemo-, radio-, and immune therapy. If the anti-angiogenic agent is too potent or the dose is too high, the balance can tip in the other direction and cause excessive vessel pruning. This can result in tumor regression and/or increased hypoxia (panel 4, top). However, increased hypoxia could decrease the efficacy of various therapies and may increase metastasis. Alternatively, tumors might switch to utilizing other angiogenic molecules and begin to make abnormal vessels again (panel 4, bottom). Hence, considerable effort is directed toward blocking these molecules.

Other mechanisms of benefit from combined anti-angiogenesis therapy and chemotherapy include: (1) anti-angiogenic agents directly killing cancer cells and sensitizing endothelial cells to cytotoxic drugs, (2) direct killing of endothelial cells by cytotoxic drugs, and/or (3) decompression of tumor vessels through killing of tumor cells by cytotoxic and/or anti-angiogenic agents, leading to improved perfusion. Anti-angiogenic agents can also impair the recruitment of bone marrow-derived progenitors, which can differentiate to endothelial cells or release pro-angiogenic molecules.

Not every cancer patient responds to anti-VEGF-targeted agents. Among various evasion mechanisms, treated tumors can release additional pro-angiogenic molecules or recruit tumor vessels via sprouting-independent mechanisms, which may be less dependent on VEGF. Tumor endothelial cells can show signs of cytogenetic abnormalities, and cancer-like stem cells can differentiate into endothelial cells—processes that may reduce the sensitivity to anti-VEGF drugs. In addition, recruitment of angiocompetent myeloid cells, activation of cancer-associated fibroblasts, or coverage of tumor vessels by thick mural cell (pericyte) coats may also render tumors insensitive to VEGF-blockade.

Though we are still striving to better understand these mechanisms in preclinical studies, the emerging clinical data from two trials indicate that the patients whose brain tumor blood perfusion levels increase during anti-VEGF therapies survive longer than the patients whose blood flow does not increase. To our knowledge, there are no clinical data showing a correlation between decreased blood perfusion and increased survival in any tumor type.

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