Tumor Angiogenesis in Colorectal Cancer

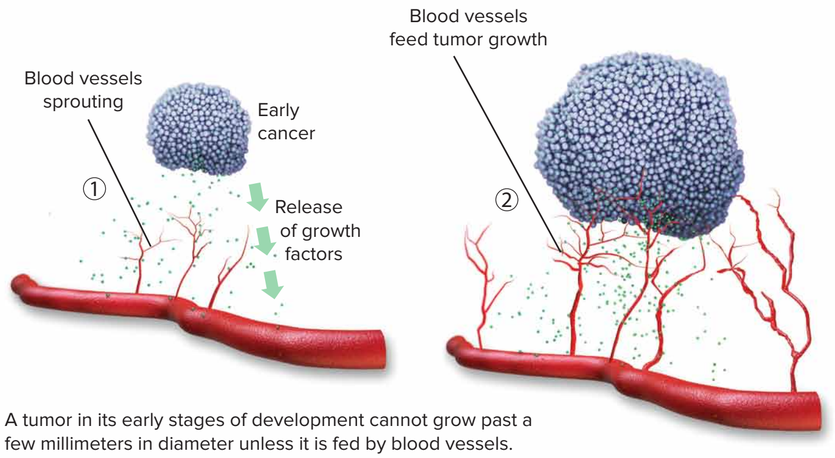
The Angiogenesis Foundation
www.scienceofcrc.org

Metastatic colorectal cancer (mCRC) is the third leading cause of cancer-related deaths in the United States. Treatment algorithms must be updated to accommodate all targeted and antiangiogenic agents as potential therapy for patients with mCRC.

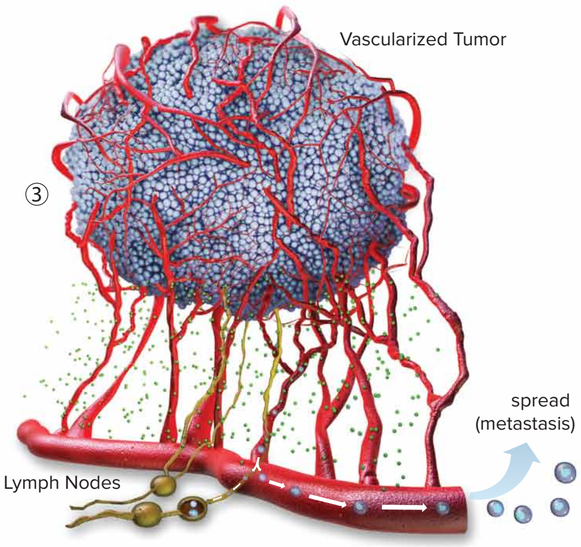
1. Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to acquired gene mutations and hypoxia.

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

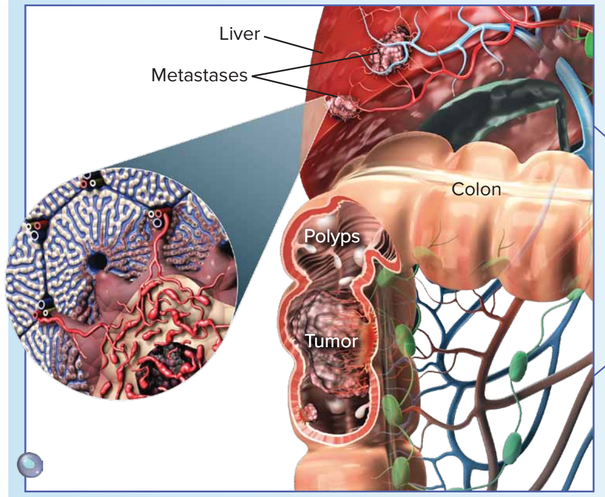
3. Tumor blood vessels are characteristically tortuous, saccular, and leaky; blood flow is uneven and chaotic, with areas of tumor necrosis, hypoxia, and acidosis.



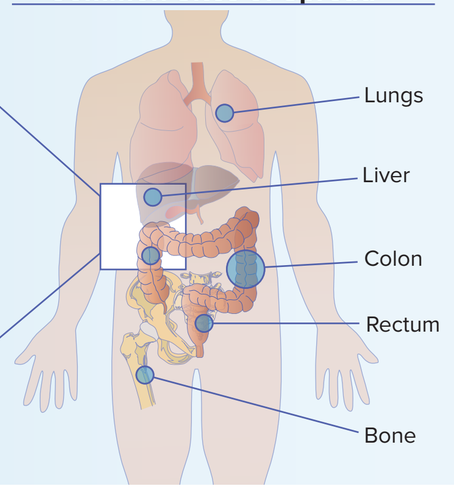
A tumor in its early stages of development cannot grow past a few millimeters in diameter unless it is fed by blood vessels.



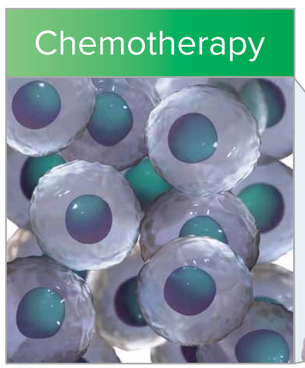
Angiogenesis in CRC liver metastases is initiated when a tumor co-opts sinusoidal endothelial cells lining the periphery of the lesion. The liver contributes abundant proangiogenic factors to the metastatic lesion.



Common Sites of Spread

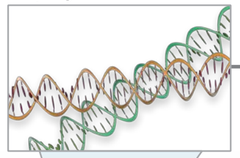


Treatments for Metastatic Colorectal Cancer

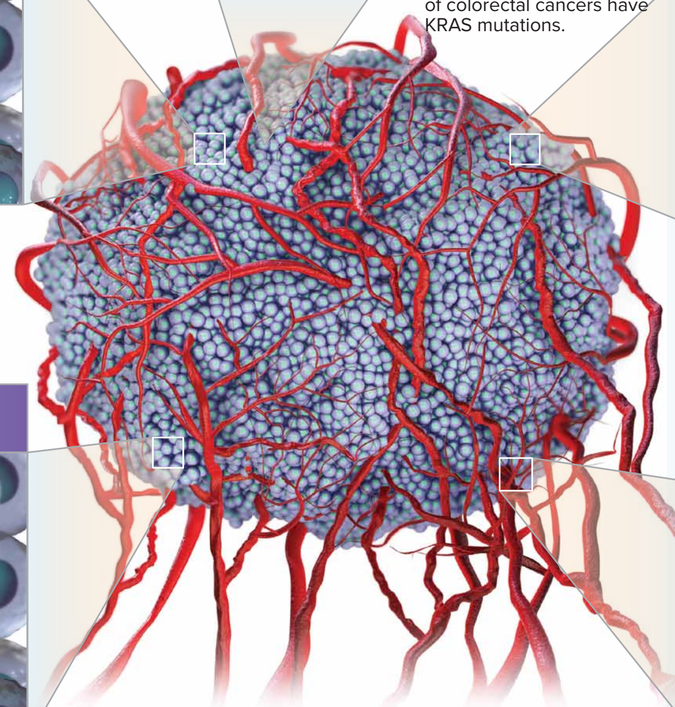


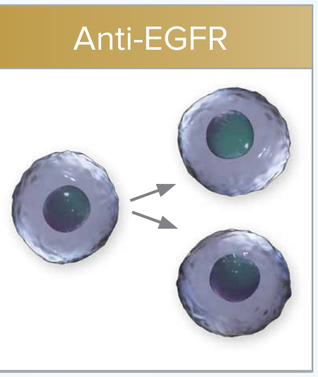
Chemotherapy attacks the cancer cells directly, causing them to die off.

Radiation therapy kills cancer cells with high-energy rays.

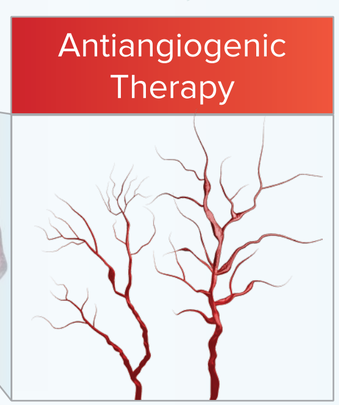


Available EGFR inhibitors are ineffective in tumors that carry mutations of the KRAS gene. Roughly 40% of colorectal cancers have KRAS mutations.





Anti-EGFR therapy attacks the growth signals that encourage proliferation of cancer cells.



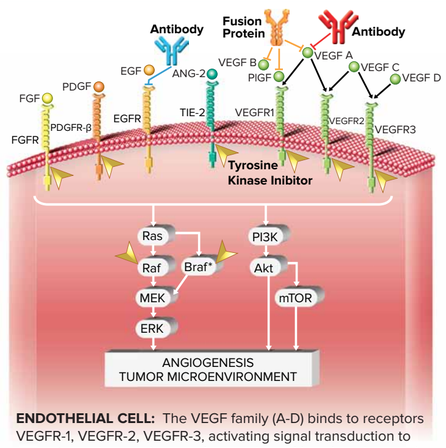
Antiangiogenic therapies attack the blood vessels that feed the tumor.

SCIENCE OF CRC

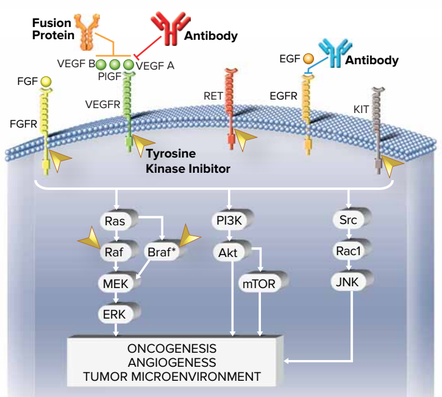
This resource was independently developed with grants from Bayer Pharma AG, Genentech, and Regeneron.

Targeted Therapies

Targeted cancer therapies halt the growth and spread of cancer by "targeting," or interfering, with specific molecules that play a role in tumor progression and growth. In addition to the targeted treatments that have already gained FDA approval, numerous other agents such as monoclonal antibodies, engineered proteins, tyrosine kinase inhibitors (TKIs) and other small molecule agents with varying mechanisms of action are currently under investigation as potential therapy for patients with mCRC.



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



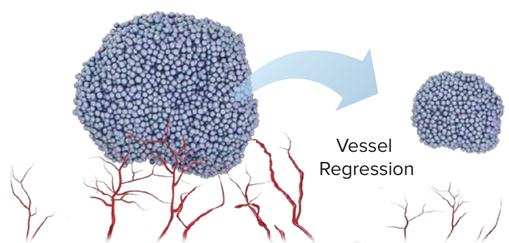
TUMOR CELL: Multiple growth factors and receptors activate signal transduction and cell cycle pathways that stimulate tumor cell growth.

ANG = Angiogenin; EGF = Epidermal Growth Factor; FGF = Fibroblast Growth Factor; PDGF = Platelet-Derived Growth Factor; PlGF = Placental Growth Factor; VEGF = Vascular Endothelial Growth Factor

Potential Outcomes of Targeted Therapies

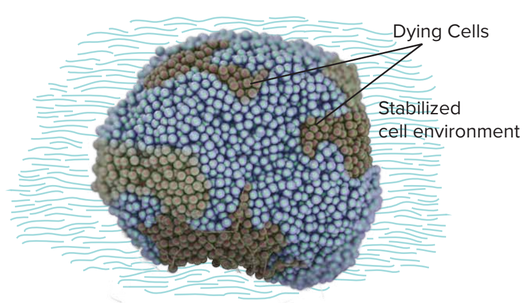
1. Tumor Shrinkage

Metastatic tumors often shrink significantly with targeted treatments. Without a blood supply, the tumors cannot sustain themselves.



2. Stop Tumor Growth

Primary tumors are also affected by targeted treatments. As the vessels feeding the tumor shrink back, cells in the tumor mass are starved for oxygen and nutrients. Tumor growth is stopped and the surrounding environment becomes more stable.



3. Disease Progression

Tumors may continue to grow despite treatment. This is called "non-response" to treatment.