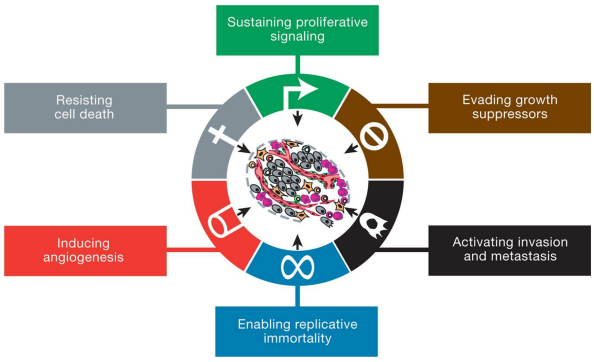
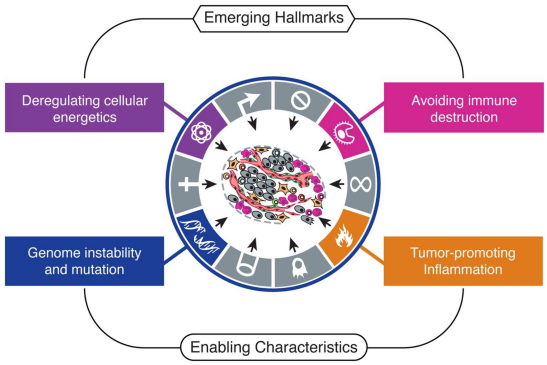
ANGIONESESIS
EMT
METASTASIS



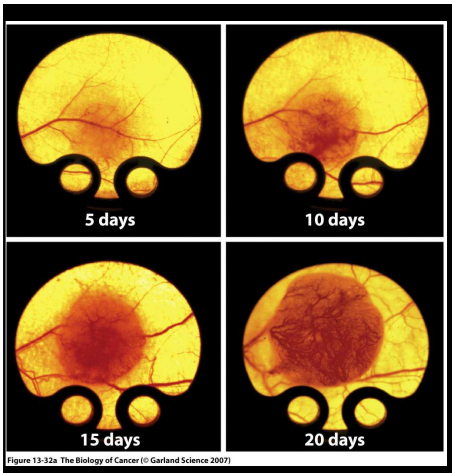
Hallmarks of Cancer: original six hallmarks, proposed by Hanahan and Weinberg in 2000, that enable tumor growth and metastasis. Provided an overview for understanding the biology of cancer.



Updated Hallmarks of Cancer: Hanahan and Weinberg in 2011 added two emerging hallmarks and two enabling characteristics that facilitate cancer devlopment.

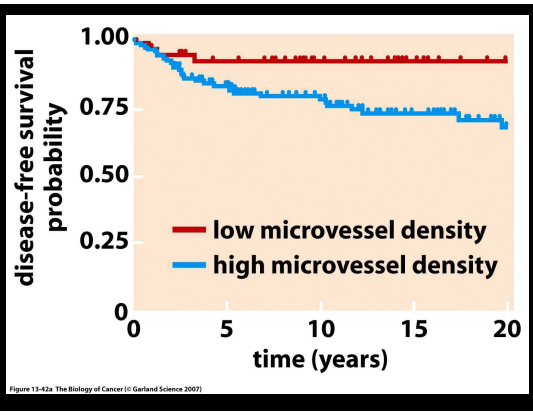
Cancer is a disease of tissues, not just cells!

- For a long time, cancer research has focused mainly on cancer cells and their defective genes.
- In many cancers, non-neoplastic cells account for up to 90% of the cells in the tumor mass.
- The “tumor stroma”, both inside the tumor mass and also surrounding it, contains these non-neoplastic cells.
- Interactions between the tumor cells and stroma cells (“heterotypic signaling”) influence tumor growth and progression.

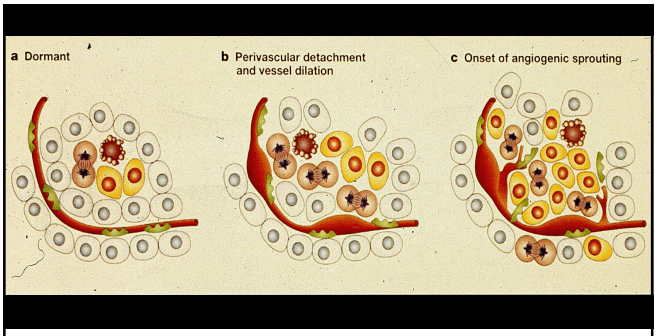


Tumor Angiogenesis

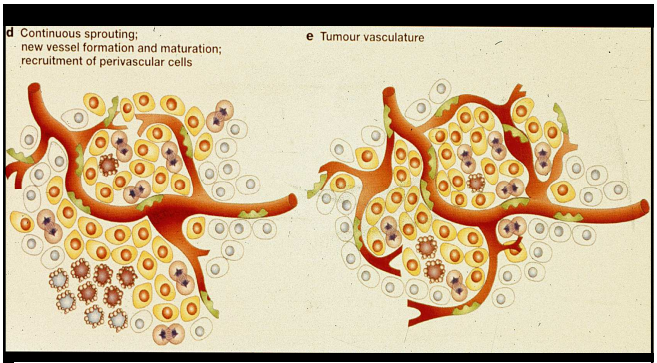
Recruitment of blood vessels by implanted tumor – first evidence of angiogenic factors in tumorigenesis



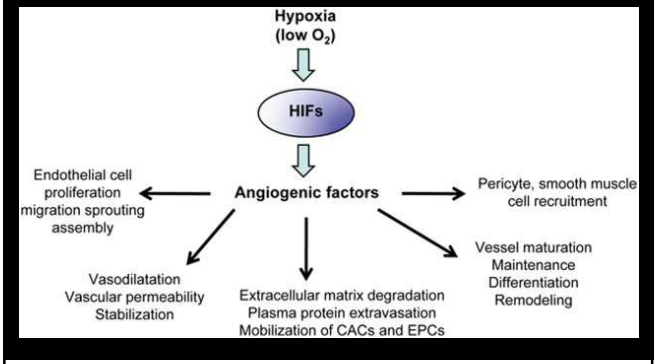
Breast Cancer: increased angiogenesis (higher microvessel density) associated with worse prognosis.



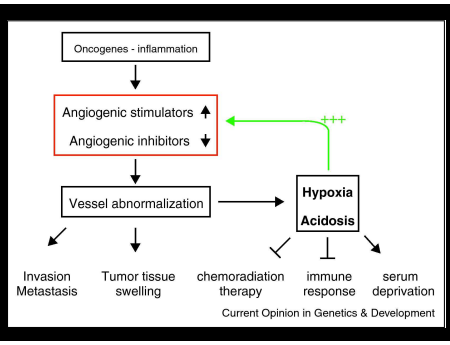
A. Most tumors start as avascular nodules (dormant). B. The "angiogenic switch" begins with pericyte detachment and vessel dilatation. C. Angiogenic sprouting occurs by endothelial migration (guided by pericytes).



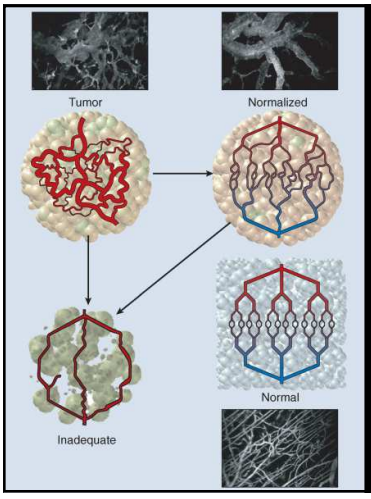
D. Angiogenic sprouting continues as endothelial cells proliferate, adhere to each other, and create lumens.
E. Sprouts fuse with other sprouts forming a complex tumor vasculature.



Hypoxia-inducible factors (HIFs): transcription factors that mediate the cellular response to physiologic hypoxia also regulate angiogenic factors, such as VEGF, which execute some of the steps in tumor angiogenesis.

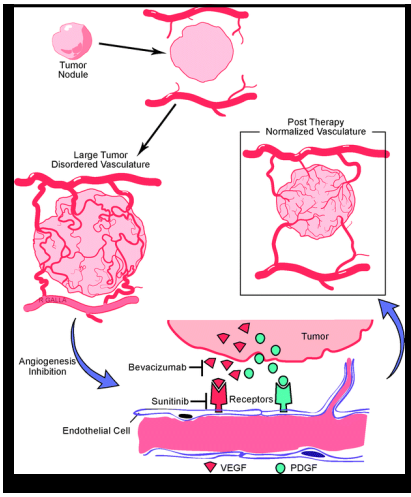


Mechanism of abnormal tumor vasculature. Angiogenic growth factors are in excess of angiogenic inhibitors leading to vessel abnormalization. This results in continual tumor hypoxia and acidosis creating a self-perpetuating cycle of abnormal angiogenesis which promotes tumor invasion and metastasis and hinders chemoradiation therapy.

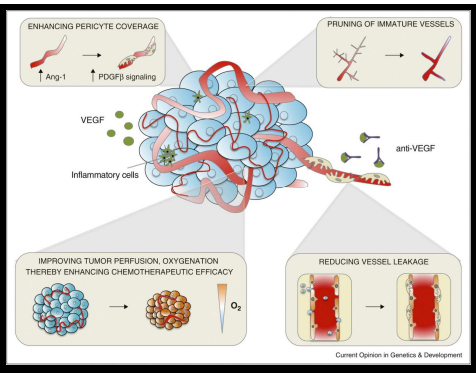


The capillaries inside of tumors are chaotic.

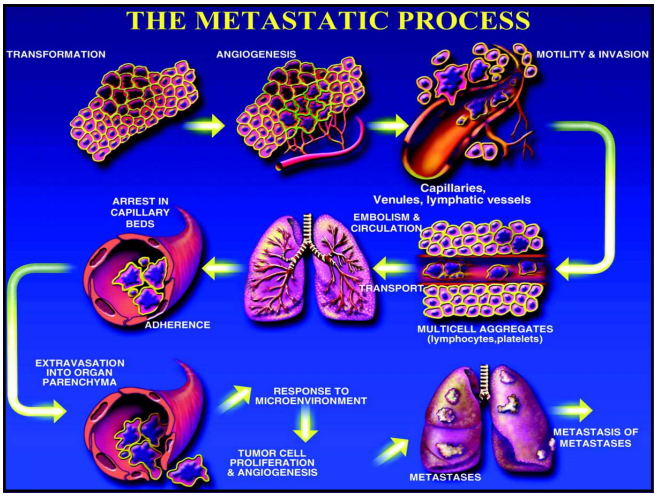
Angiogenesis inhibitors (anti-VEGF therapy) associated with "normalization" of tumor vasculature. The goal of therapy is total vessel collapse and inadequate support for tumor growth. Normalization of the tumor vasculature enhances chemotherapeutic drug delivery.

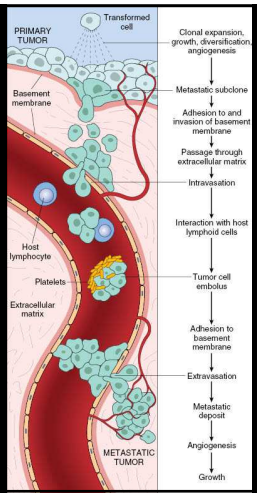


Tumor angiogenesis and therapeutic angiogenesis inhibitors: Tumors secrete VEGF and PDGF. Current clinical approaches include bevacizumab (Avastatin), an antibody against VEGF, and sunitinib (Sutent) a small molecule inhibitor of the VEGF receptor,

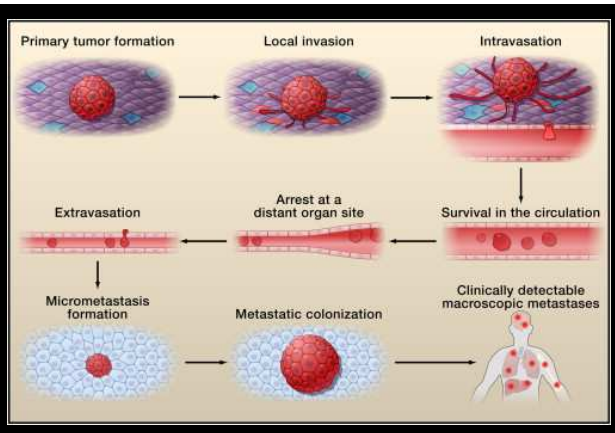


Anti-VEGF therapy induces normalization of the tumor vasculature. It increases pericyte coverage (thru Ang-1 and PDGFβ signaling), destroys existing vessels and prevents new vessel growth ("vessel pruning"), improves tumor perfusion and oxygenation, and enhances drug delivery.

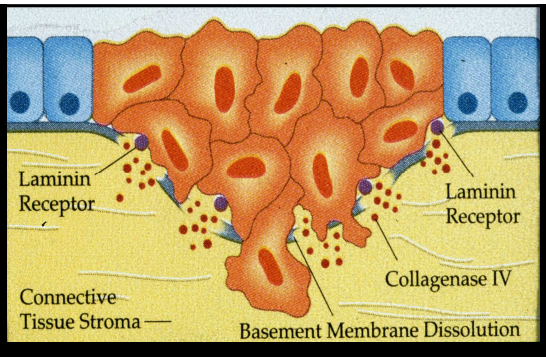




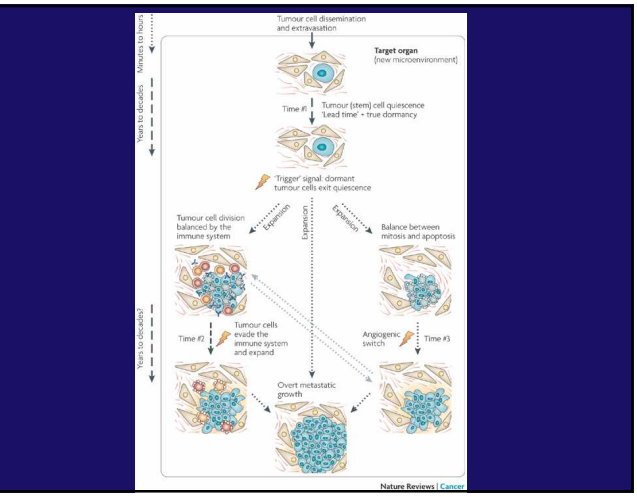
Metastatic cascade: hematogenous spread of a tumor

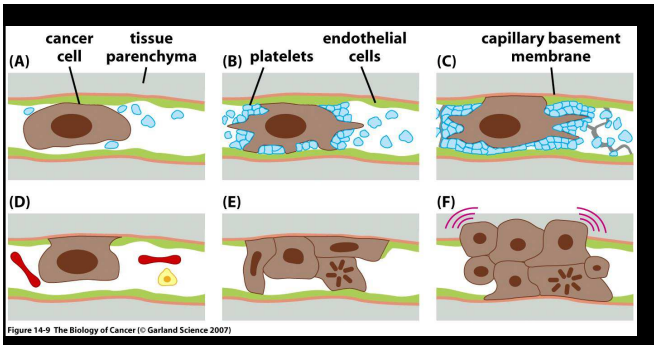


Invasion –Metastasis Cascade



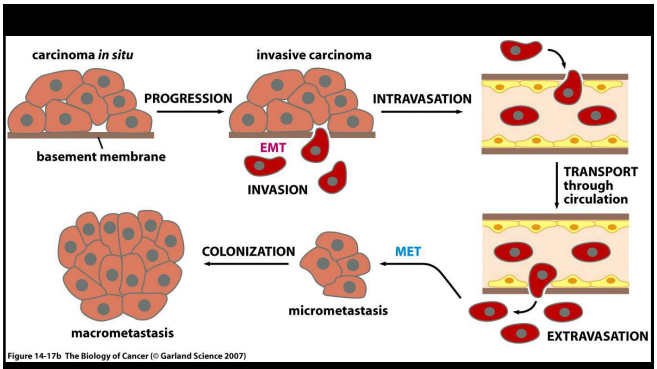
Invasion: Tumors cells, secrete enzymes, such as metalloproteinases, (Type IV collagenase) that degrade the basement membrane and express high levels of laminin and fibronectin receptors, that mediate ECM attachment.



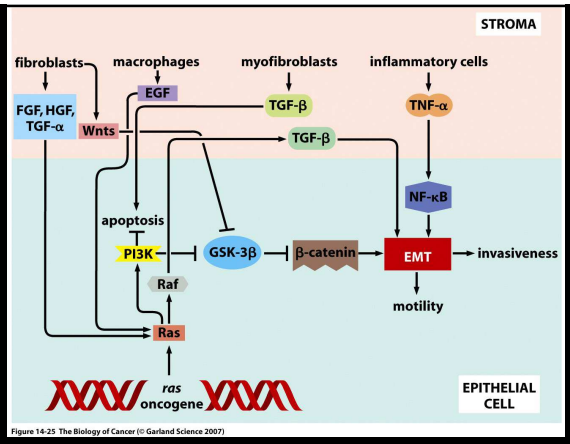


Extravasation of Cancer Cells

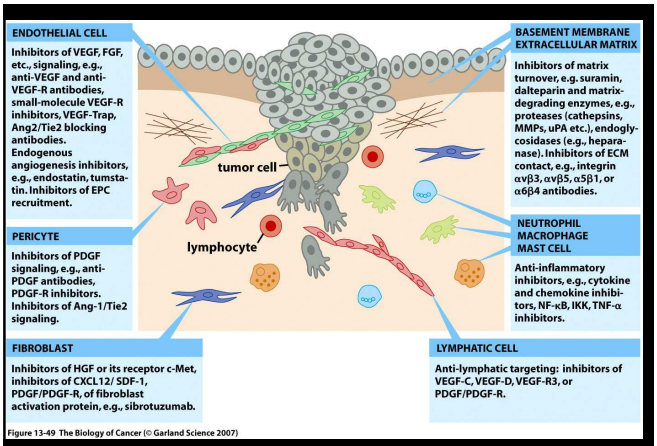
Cancer cells become trapped in capillaries, microthrombi are formed, endothelial cells are pushed aside and cancer cells contact basement membrane, cancer cell proliferates, and eventually tumor cells break through the basement membrane.



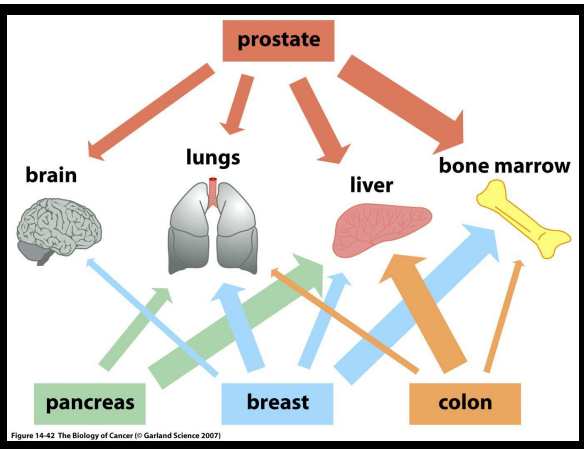
Concept of reversibility of epithelial-mesenchymal transition (EMT).



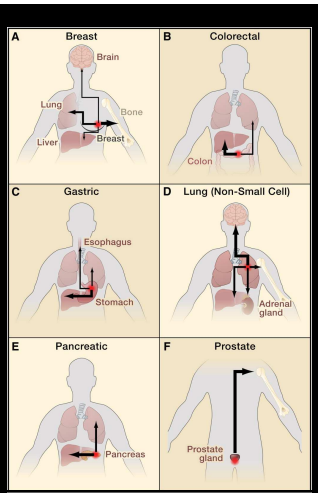
Signals that mediate EMT



Heterotypic Interactions: Targets for Cancer Therapy



Primary cancers and their metastatic tropisms



Metastatic Tropism: thickness of black lines reflects the relative frequencies in which a primary tumor type metastasizes to the indicated distant organ site)

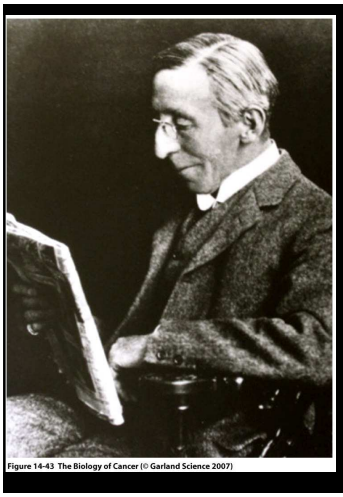


Figure 14-43 The Biology of Cancer (© Garland Science 2007)

Stephen Paget: British physician proposed the "seed and soil" hypothesis in 1889. He believed that the non-random nature of metastasis depends on an interaction between the cancer cell (*seed*) and a specific organ micro-environment (*soil*).