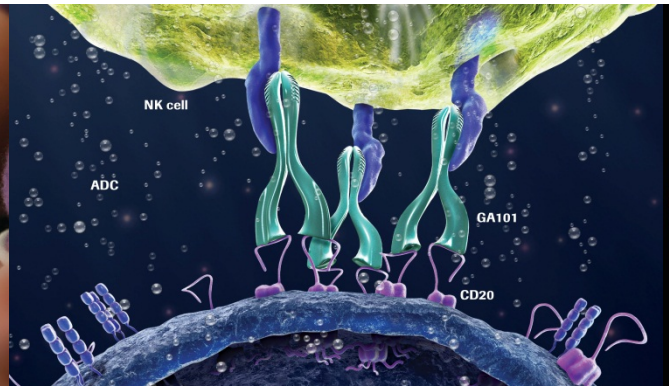
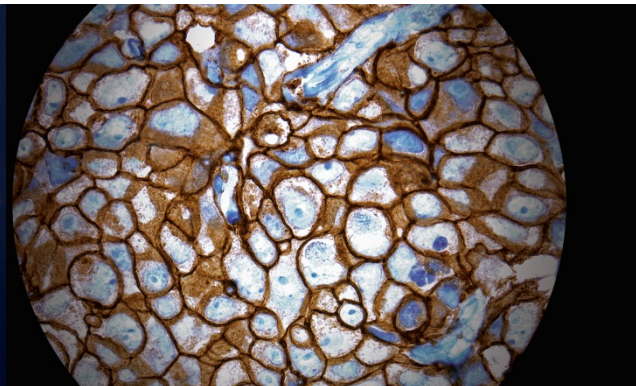
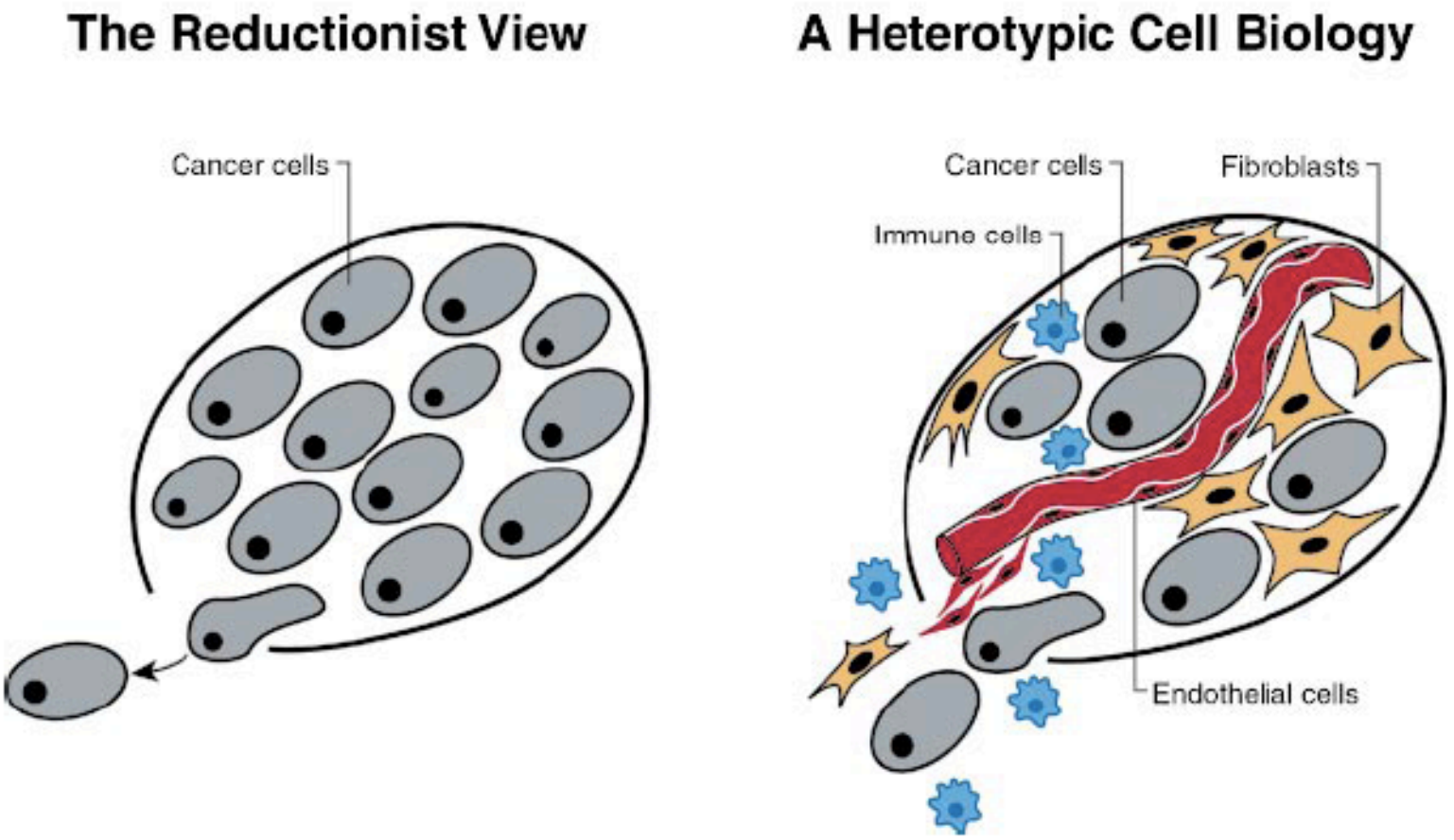
Angiogenesis and Inflammation in the Tumor Microenvironment



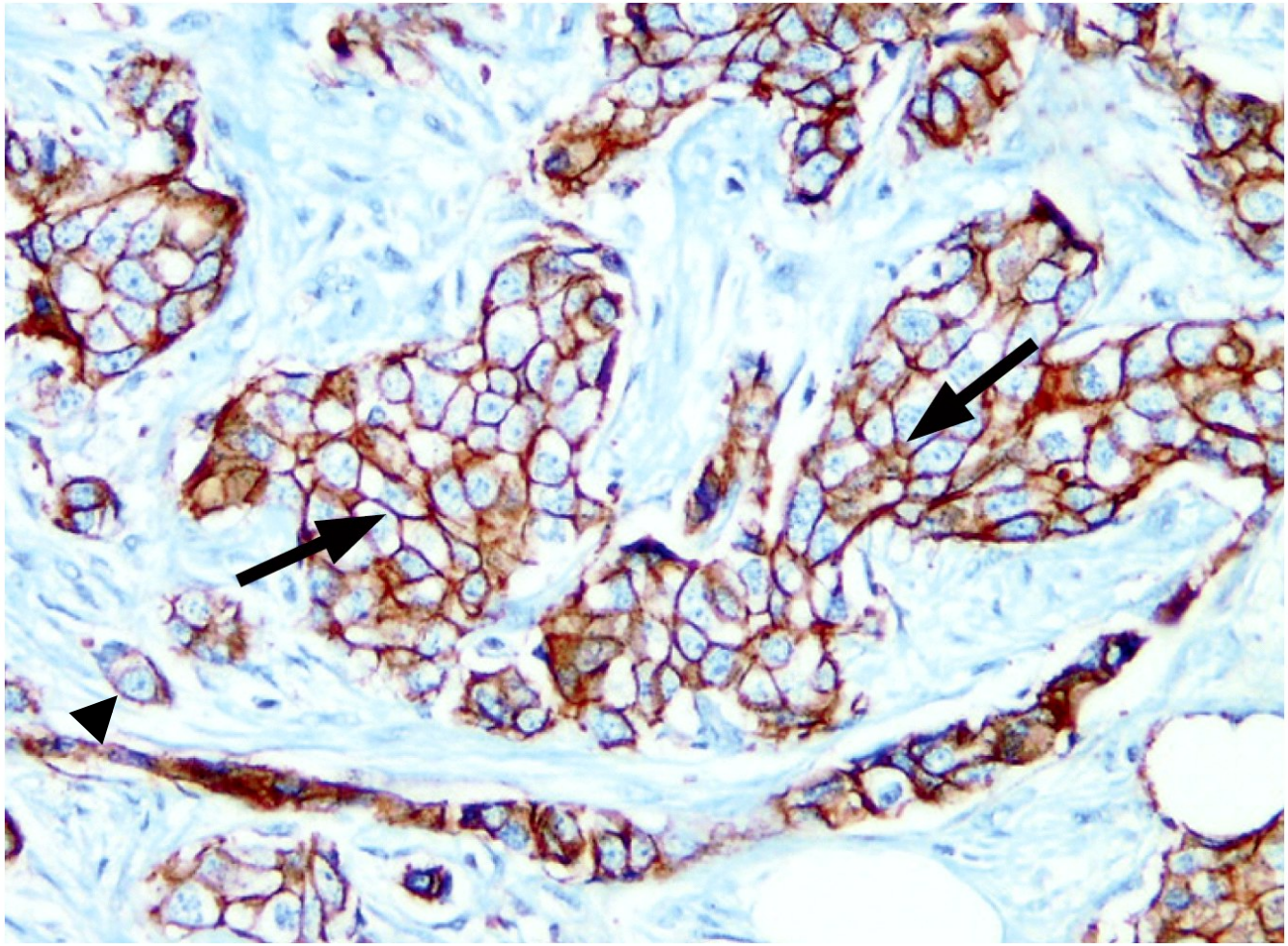


Tumors are not bags of cancer cells but rather "outlaw" complex organs



TUMOR: Cancer cells + Stromal cells + ECM

Stromal cell components of carcinomas



Invasive breast carcinoma

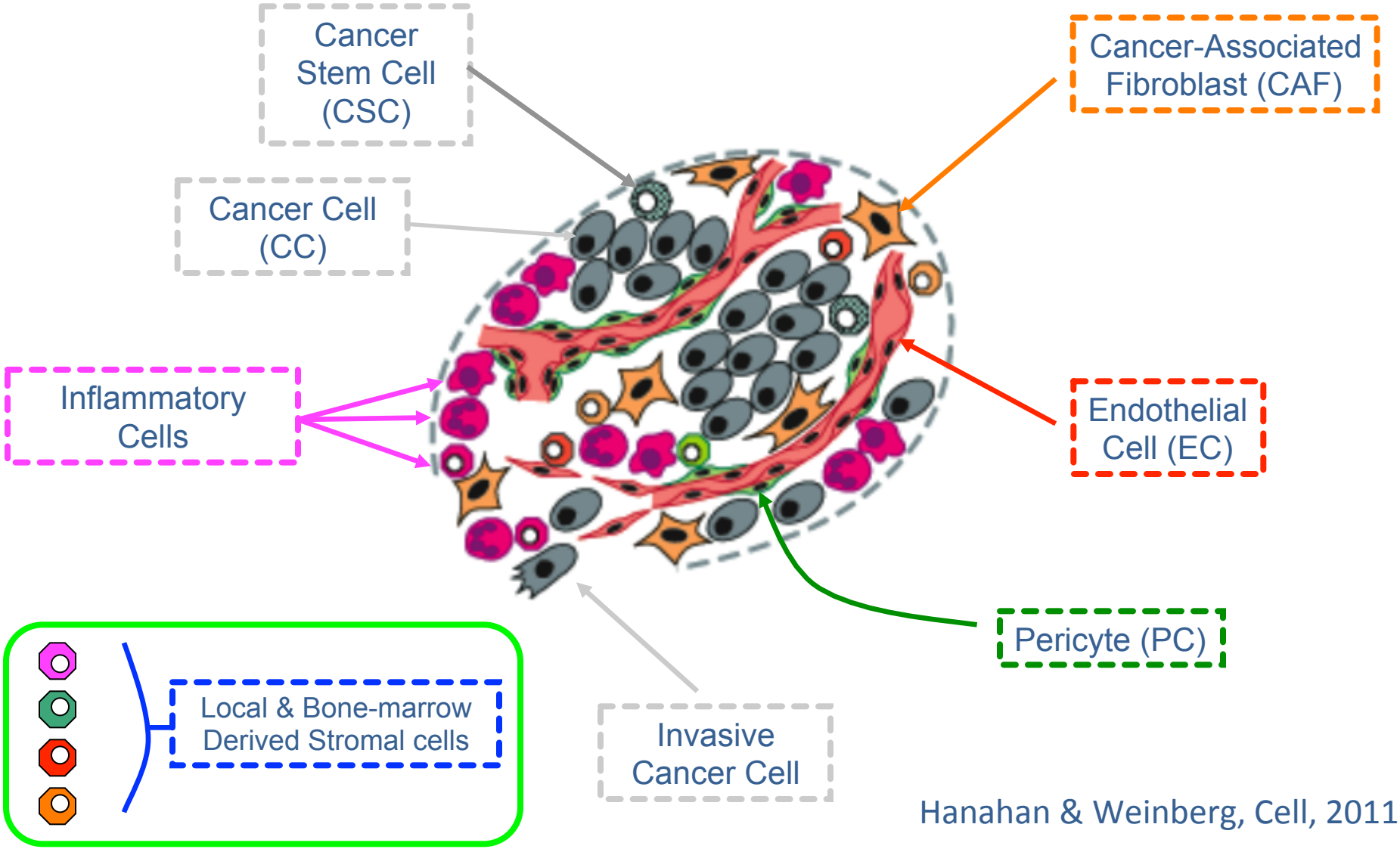
Cancer cells: brown (**arrows**)

Stromal cells / ECM: **blue**.

Note the very abundant tumor stroma in this invasive carcinoma. Single cancer cells invade the stroma (**arrowhead**).

Figure 13.1a *Weinberg, The Biology of Cancer* (© Garland Science 2007)

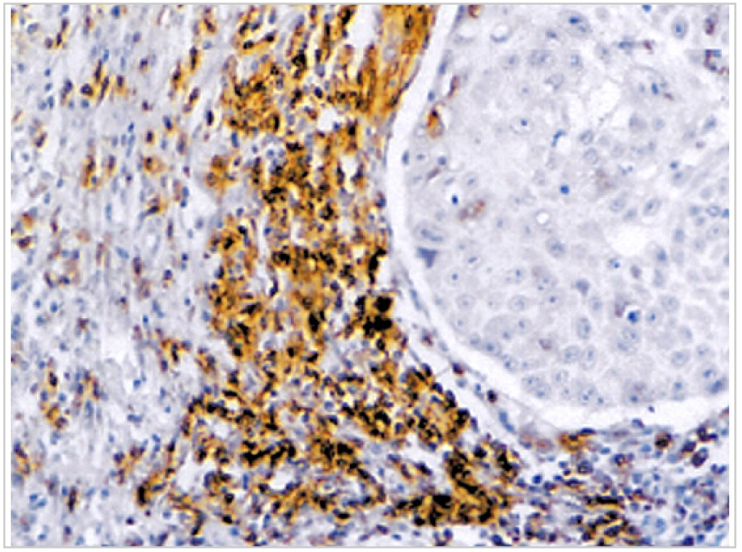
Multiple “normal” cell types are present in tumors



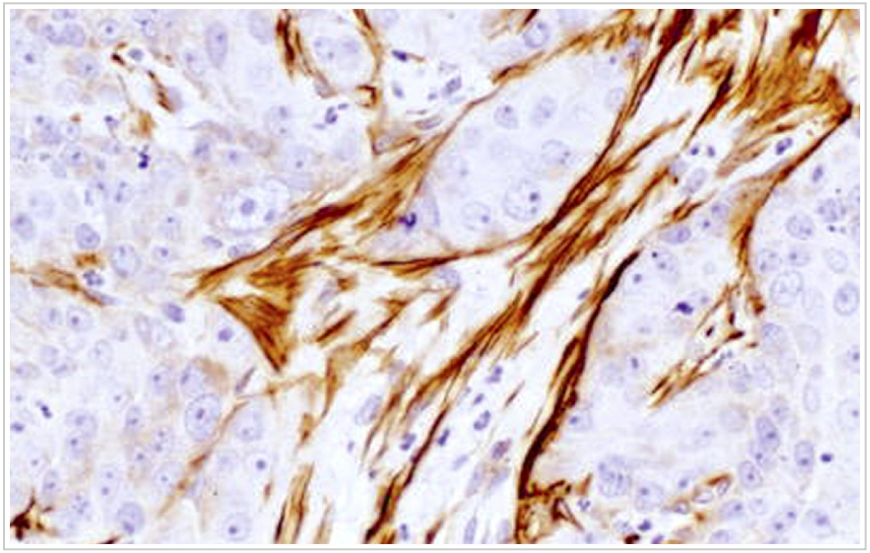
Hanahan & Weinberg, Cell, 2011

Stromal cell components of carcinomas

T lymphocytes (CD4+)



Fibroblasts (alpha-SMA+)



Monocytes/macrophages (CD11b+)

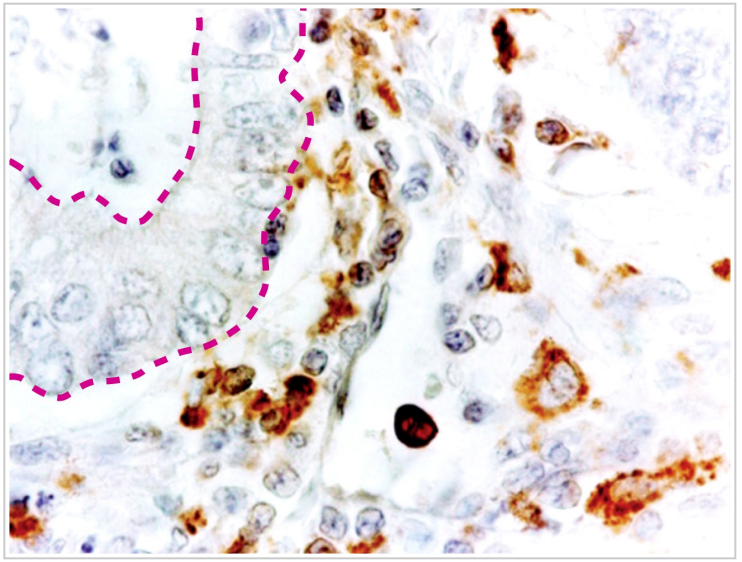
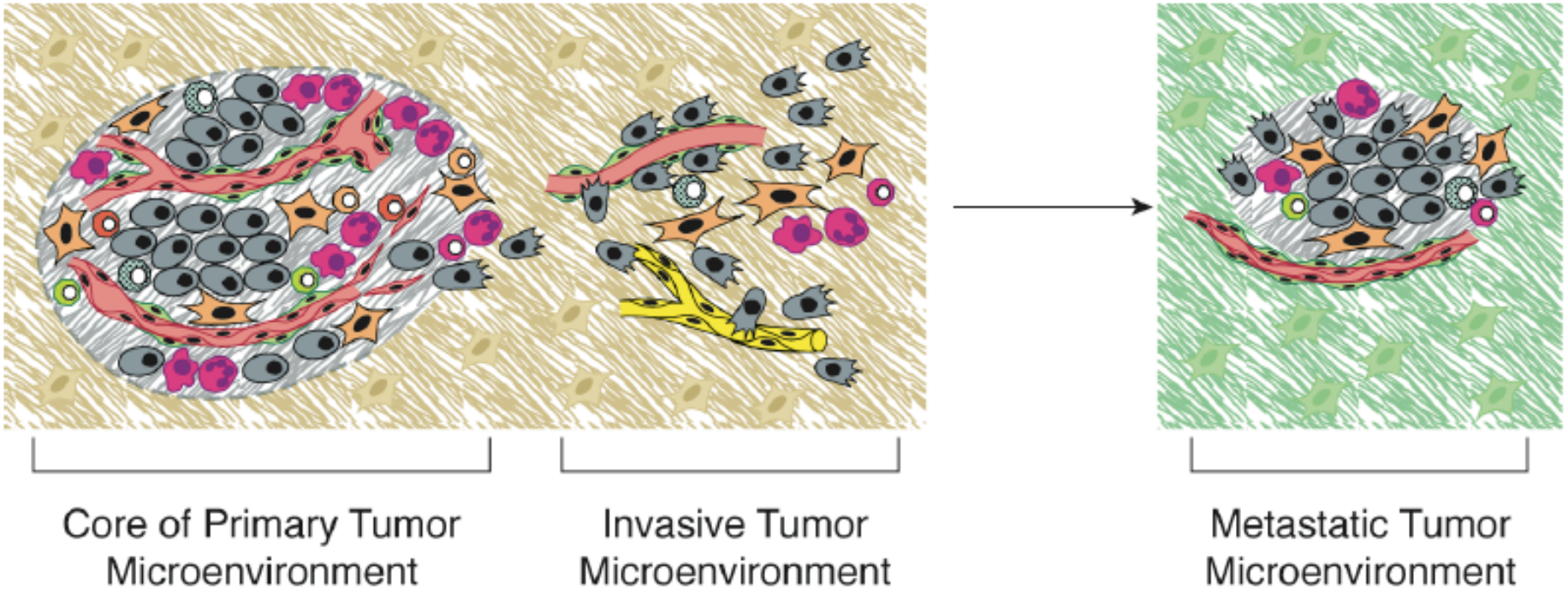


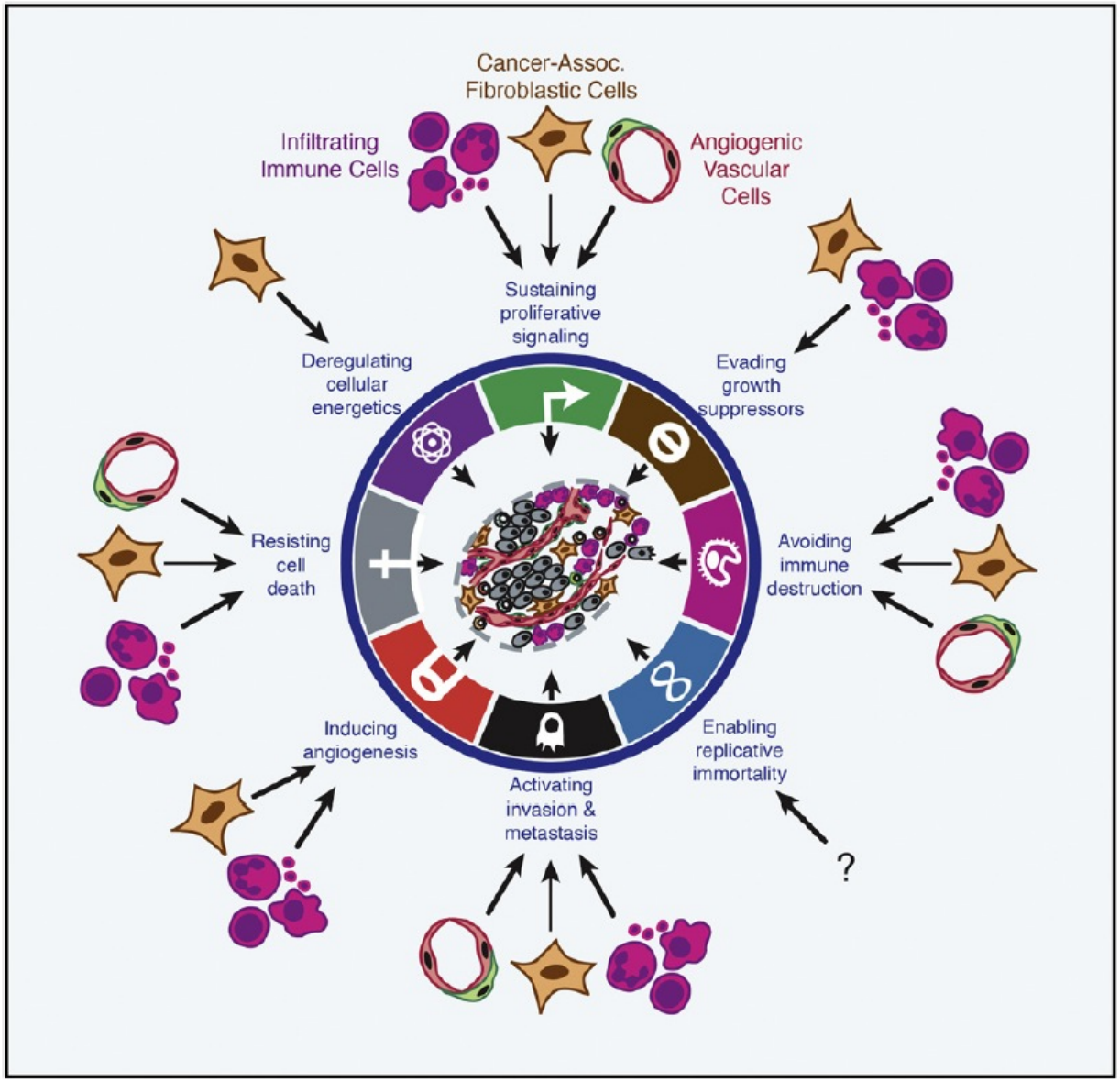
Figure 13.3a *Weinberg, The Biology of Cancer* (© Garland Science 2007)

The tumor microenvironment evolves during malignant progression



Hanahan & Weinberg, Cell, 2011

Stromal cells modulate the hallmarks of cancer

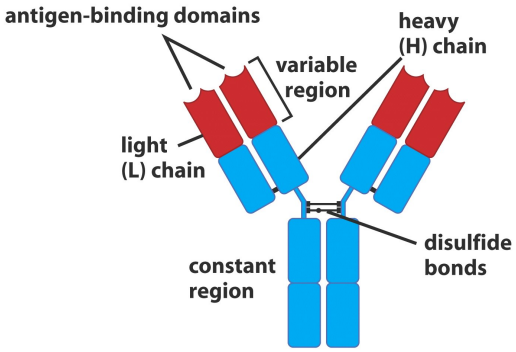


Hanahan & Coussens, Cancer Cell, 2012

Inflammation and Cancer

Some basic concepts in immunology….

Functions of antibodies (immunoglobulins)



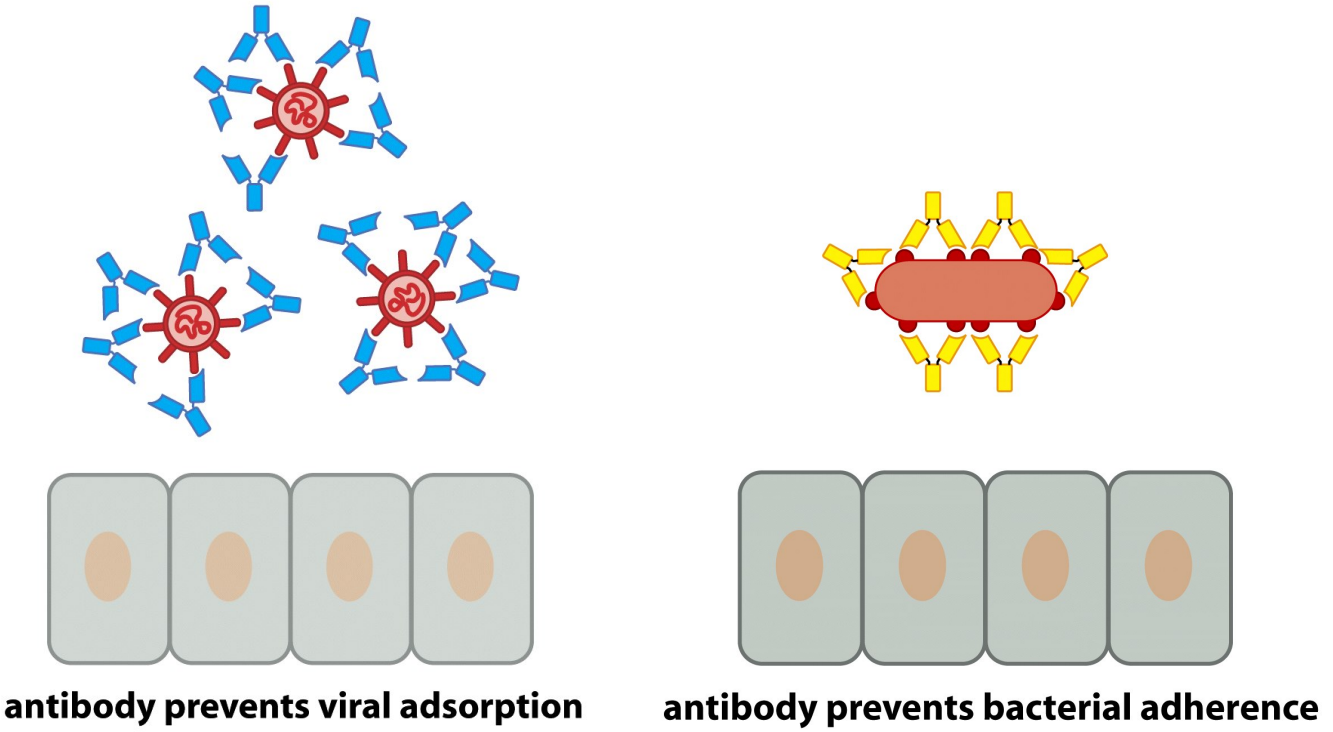
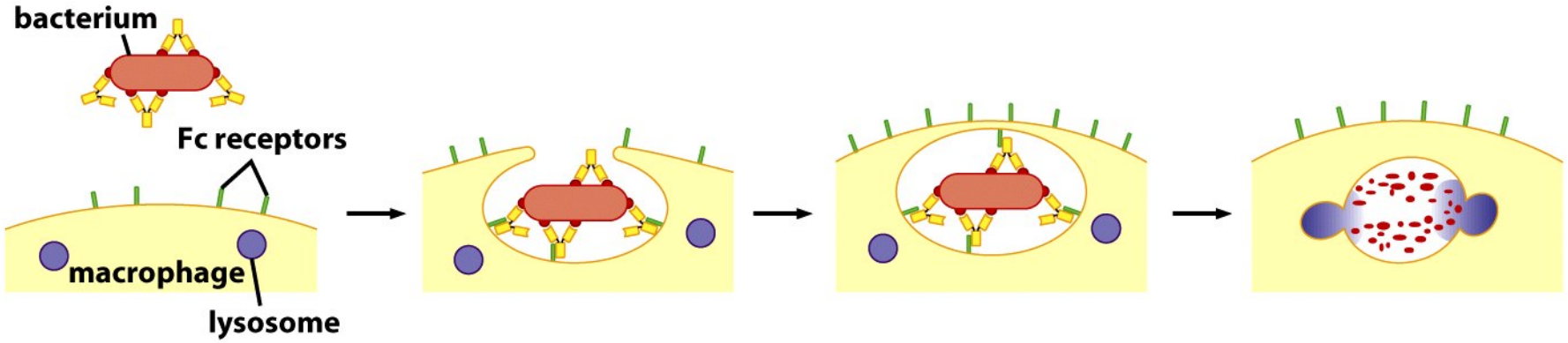


Figure 15.2b *The Biology of Cancer* (© Garland Science 2007)

Coating of pathogens or cells by antibodies stimulates their elimination by INNATE IMMUNE CELLS

Phagocytosis by macrophages (antibody-directed cellular phagocytosis, ADCP)



Lysis by NK cells

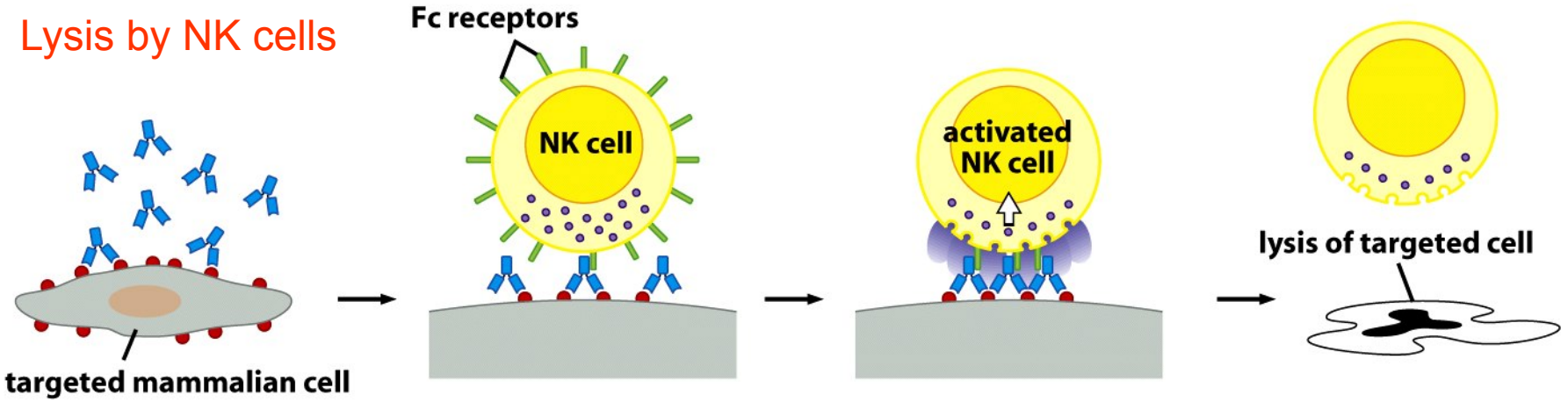
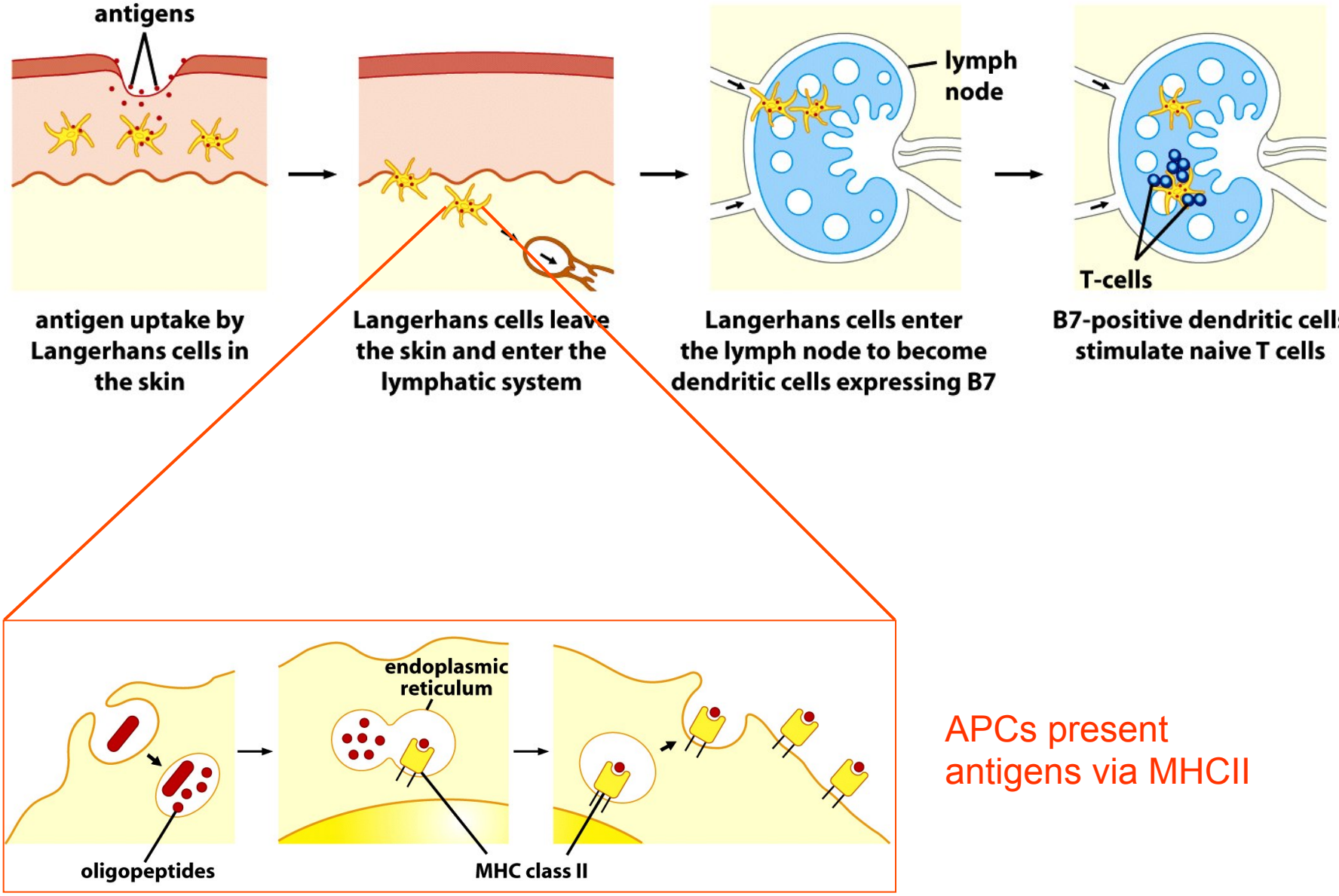


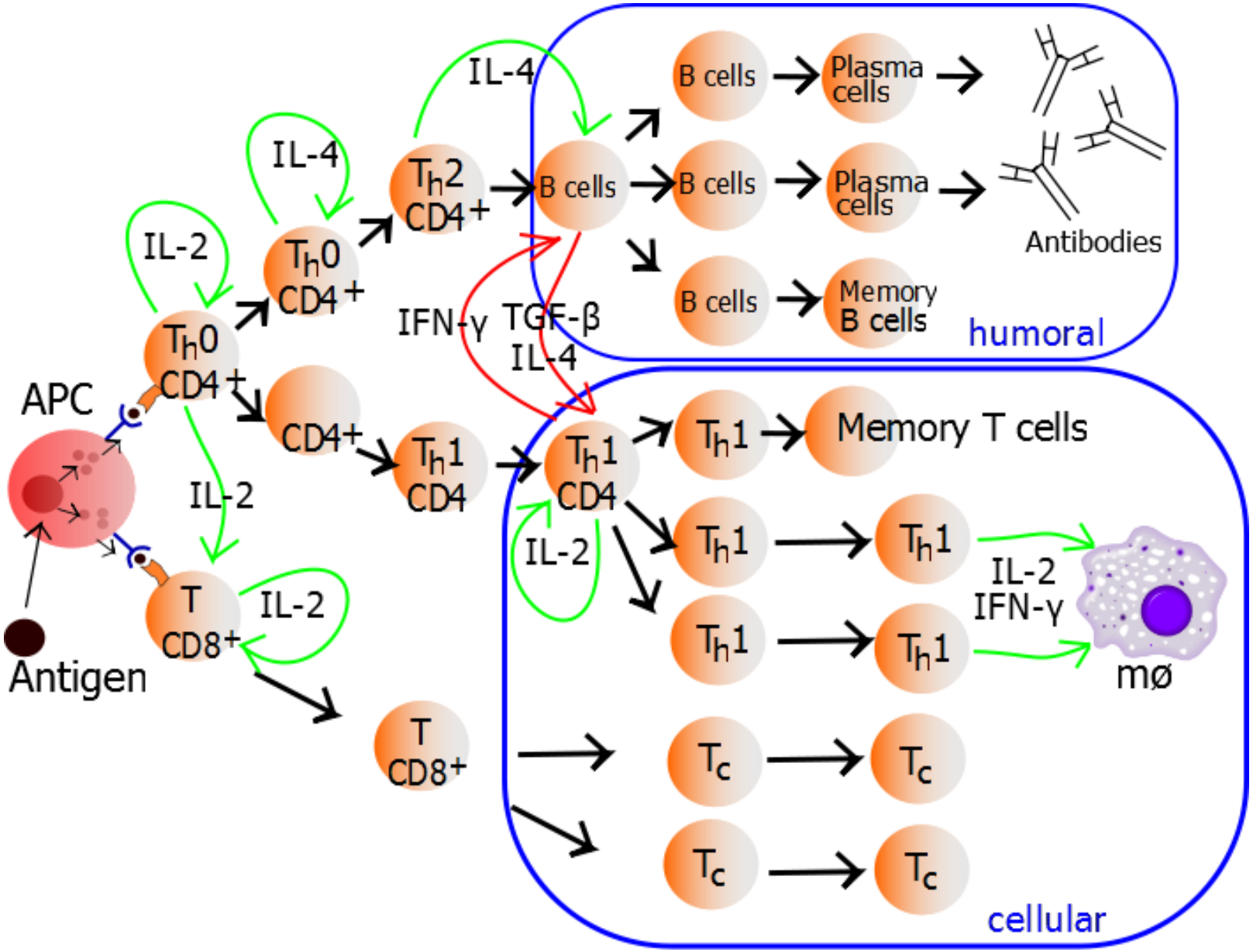
Figure 15.3b *The Biology of Cancer* (© Garland Science 2007)

Antigen uptake by APCs like DCs stimulates T-cells to mount ADAPTIVE IMMUNE RESPONSES

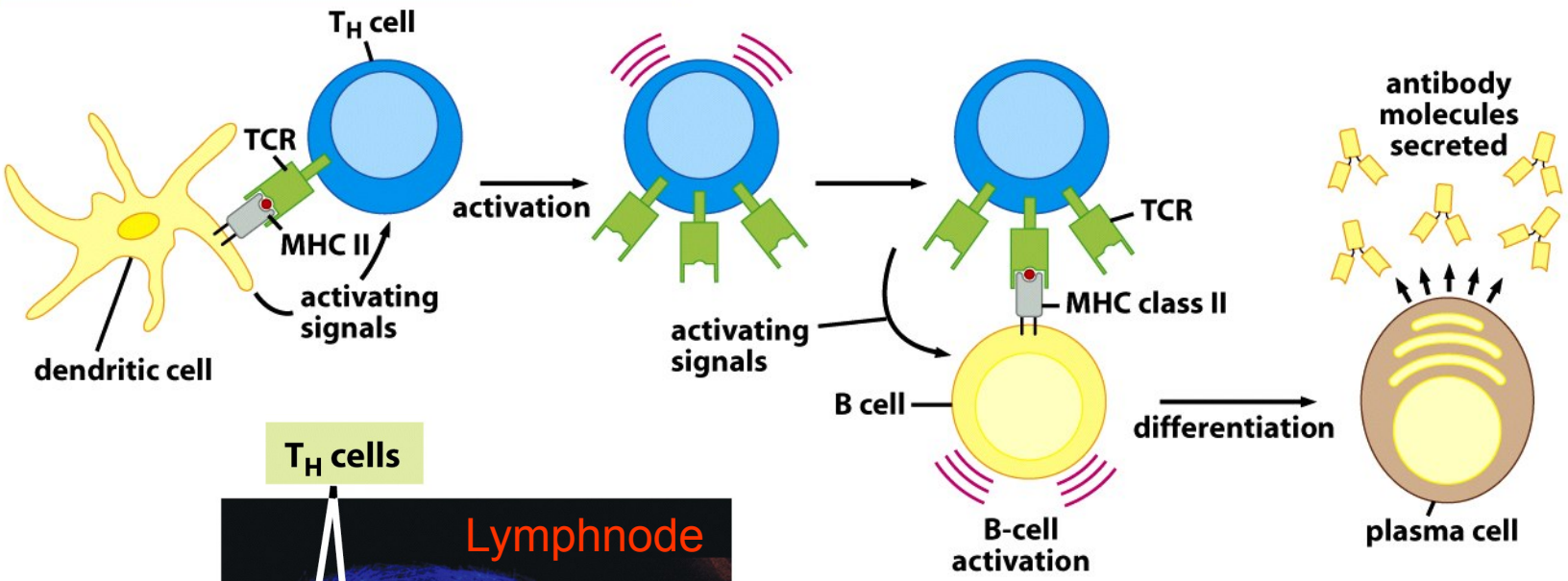


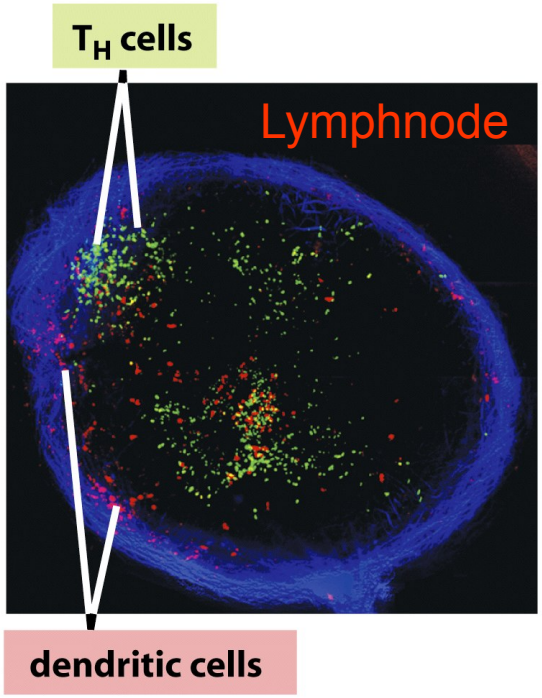
APCs present antigens via MHCII

T-cells


IL-4
IL-4
IL-2
IL-2
IL-2
IL-2
IL-2
IL-4
IFN-γ
TGF-β
IL-4
APC
Antigen
T_h0 CD4+
T_h0 CD4+
CD4+
T_h2 CD4+
T_h1 CD4
T_h1 CD4
T CD8+
T CD8+
B cells
B cells
B cells
Plasma cells
Plasma cells
Memory B cells
Antibodies
humoral
T_h1
T_h1
T_h1
T_h1
T_h1
Memory T cells
IL-2
IFN-γ
mø
T_c
T_c
T_c
T_c
cellular

Adaptive humoral responses

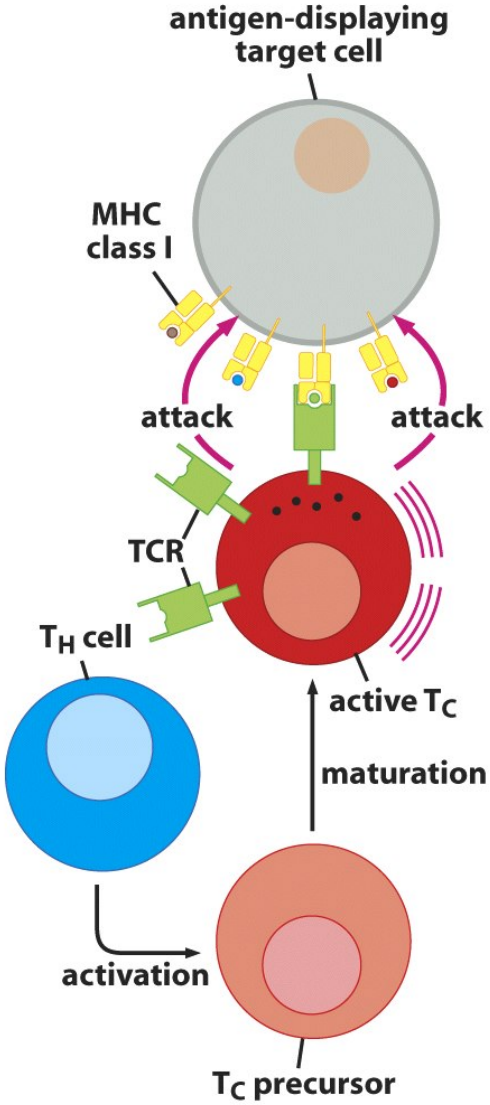




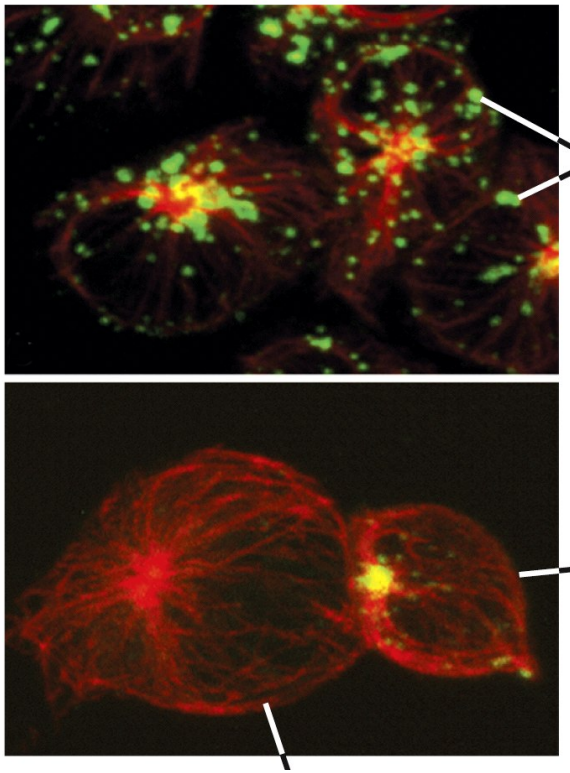
DC → TH cell → B cell → Plasma cell

Figure 15.8b *The Biology of Cancer* (© Garland Science 2007)

Adaptive cytotoxic responses



ALL CELLS can present antigens via MHCI



Lytic granules (perforin, granzymes) are scattered in the T_C cell cytoplasm

Upon contact with the target cell, the lytic granules localize at the cells' contact, are released, and kill the target cell

Figure 15.11 *The Biology of Cancer* (© Garland Science 2007)

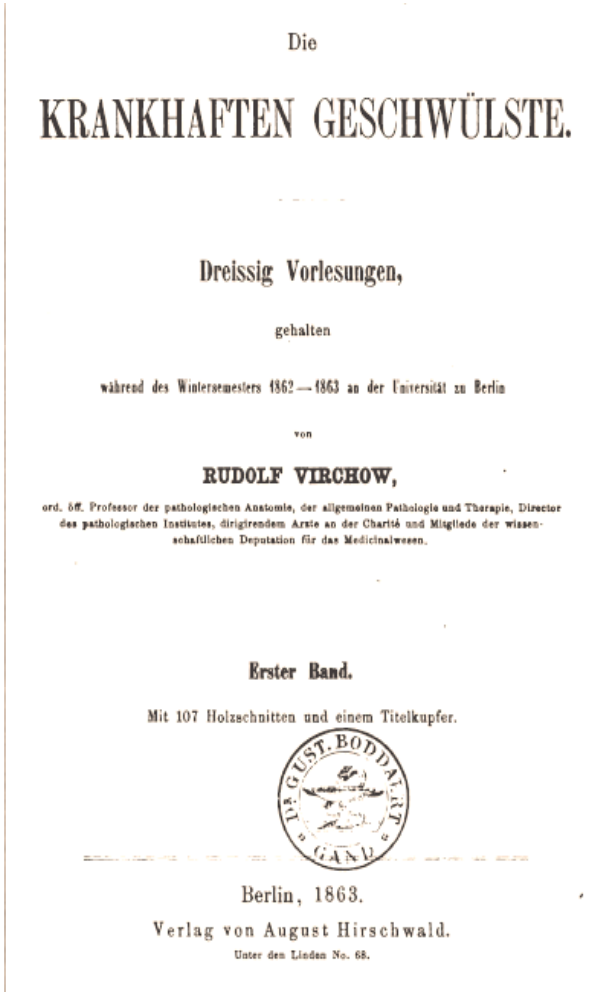
Tumor initiators and promoters

Tumor initiator: Generally a mutagen, causes genetic or epigenetic changes (mutations) in normal cells that are necessary (but often not sufficient) for tumor development.

Tumor promoter: Fosters the growth (proliferation) of "initiated" cancer cells, enabling their acquisition of additional features, also genetic, leading to cancer. A tumor promoter may not be a mutagen. **Inflammation** is a typical tumor promoter.

Rudolf Virchow, 1863

Virchow first noted the association of tumors with chronically inflamed tissues (tissues characterized by unusually high numbers of infiltrating inflammatory cells, or leukocytes)



Die

KRANKHAFTEN GESCHWÜLSTE.

Dreissig Vorlesungen,

gehalten

während des Wintersemesters 1862—1863 an der Universität zu Berlin

von

RUDOLF VIRCHOW,

ord. öff. Professor der pathologischen Anatomie, der allgemeinen Pathologie und Therapie, Director des pathologischen Institutes, dirigirendem Arzte an der Charité und Mitgliede der wissenschaftlichen Deputation für das Medicinalwesen.

Erster Band.

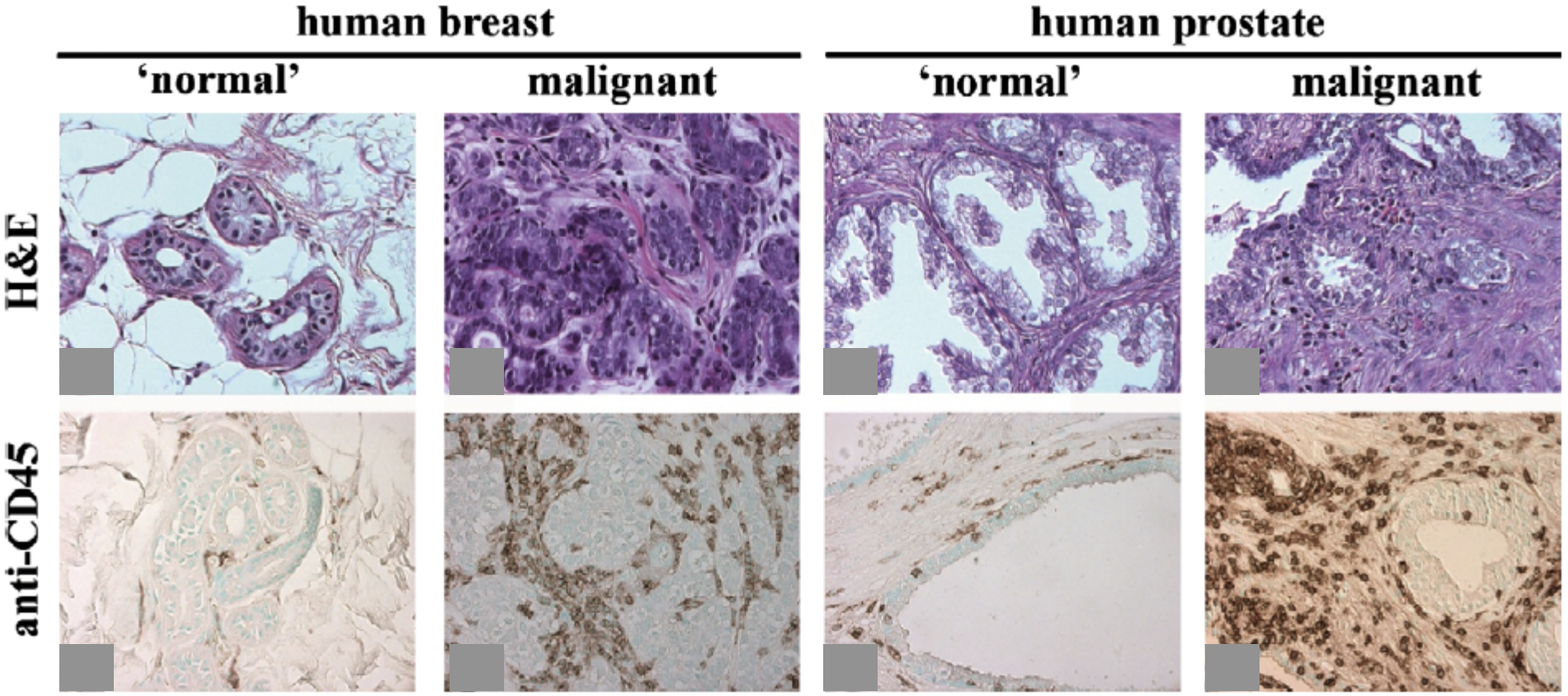
Mit 107 Holzschnitten und einem Titelkupfer.

Berlin, 1863.

Verlag von August Hirschwald.

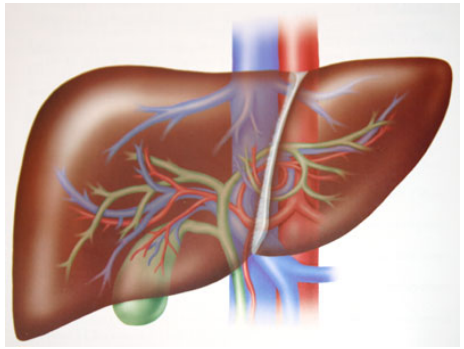
Unter den Linden No. 68.

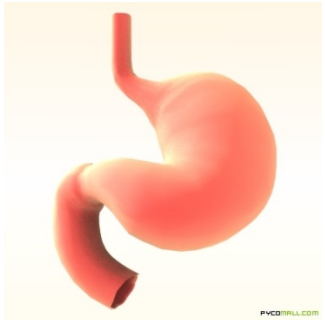
Human tumors are heavily infiltrated by leukocytes (inflammatory/immune cells)



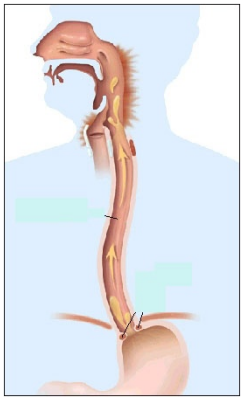
CD45: total leukocytes

Adapted from van Kempen *et al.*, *Eur J Cancer*, 2006





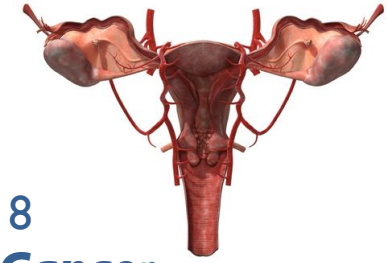
H. pylori → Gastritis
Gastric Cancer



Viral hepatitis / Liver cirrhosis
→ ***Hepatocellular Carcinoma***

Inflammation & Cancer

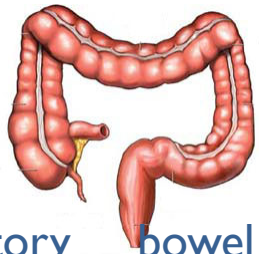
Reflux → Esophagitis
Esophageal Cancer



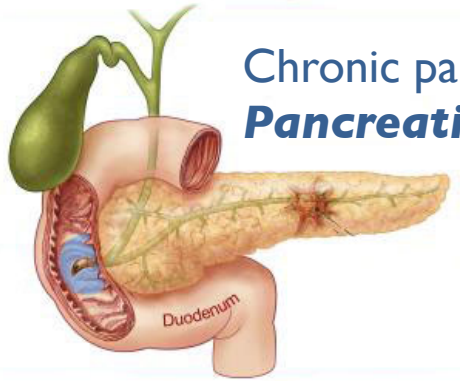
HPV-16 / 18
Cervical Cancer

Recurrent cholangitis
Cholangiocellular Carcinoma

Recurrent gallstones
Gallbladder Carcinoma

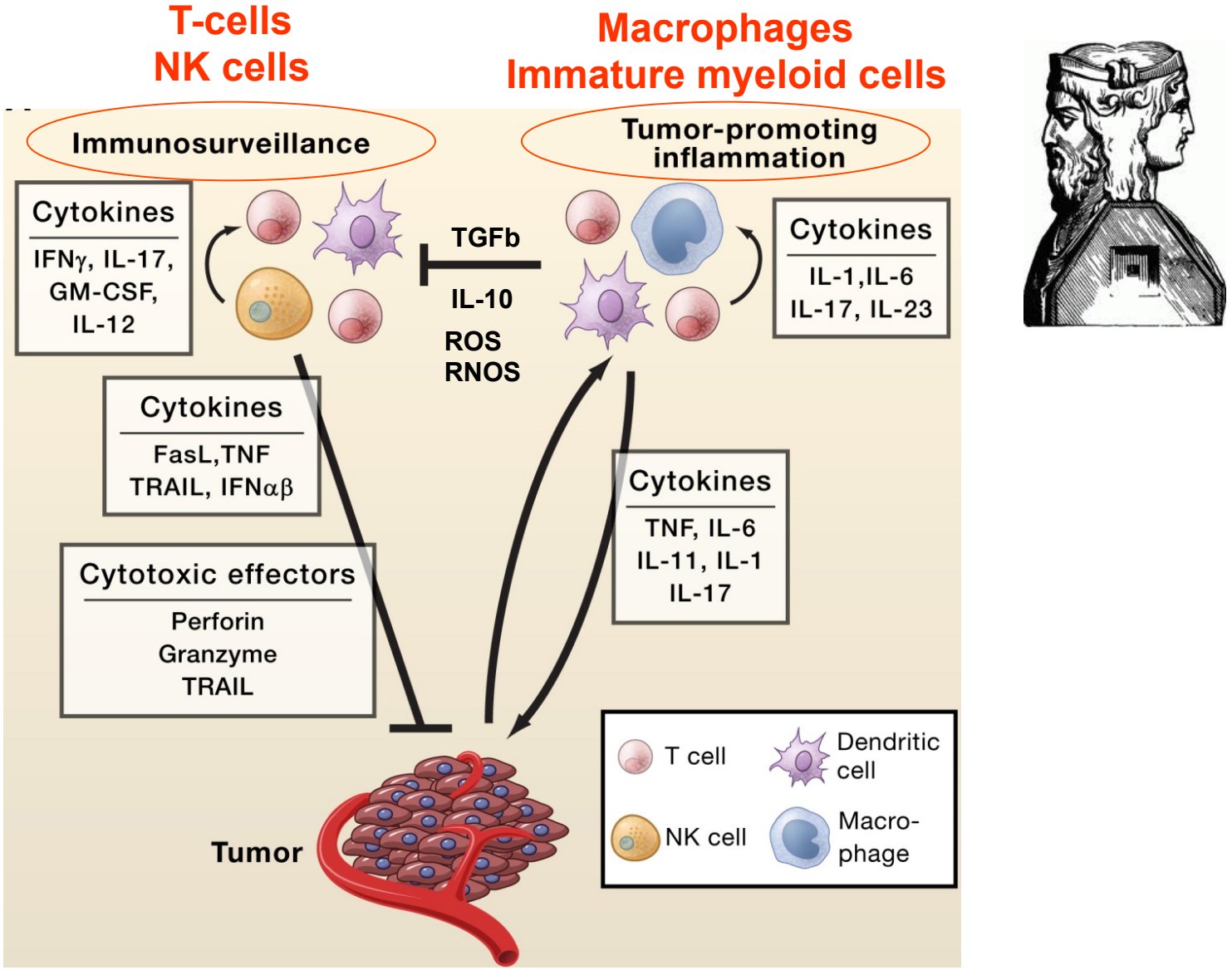


Inflammatory bowel disease
Colorectal Cancer



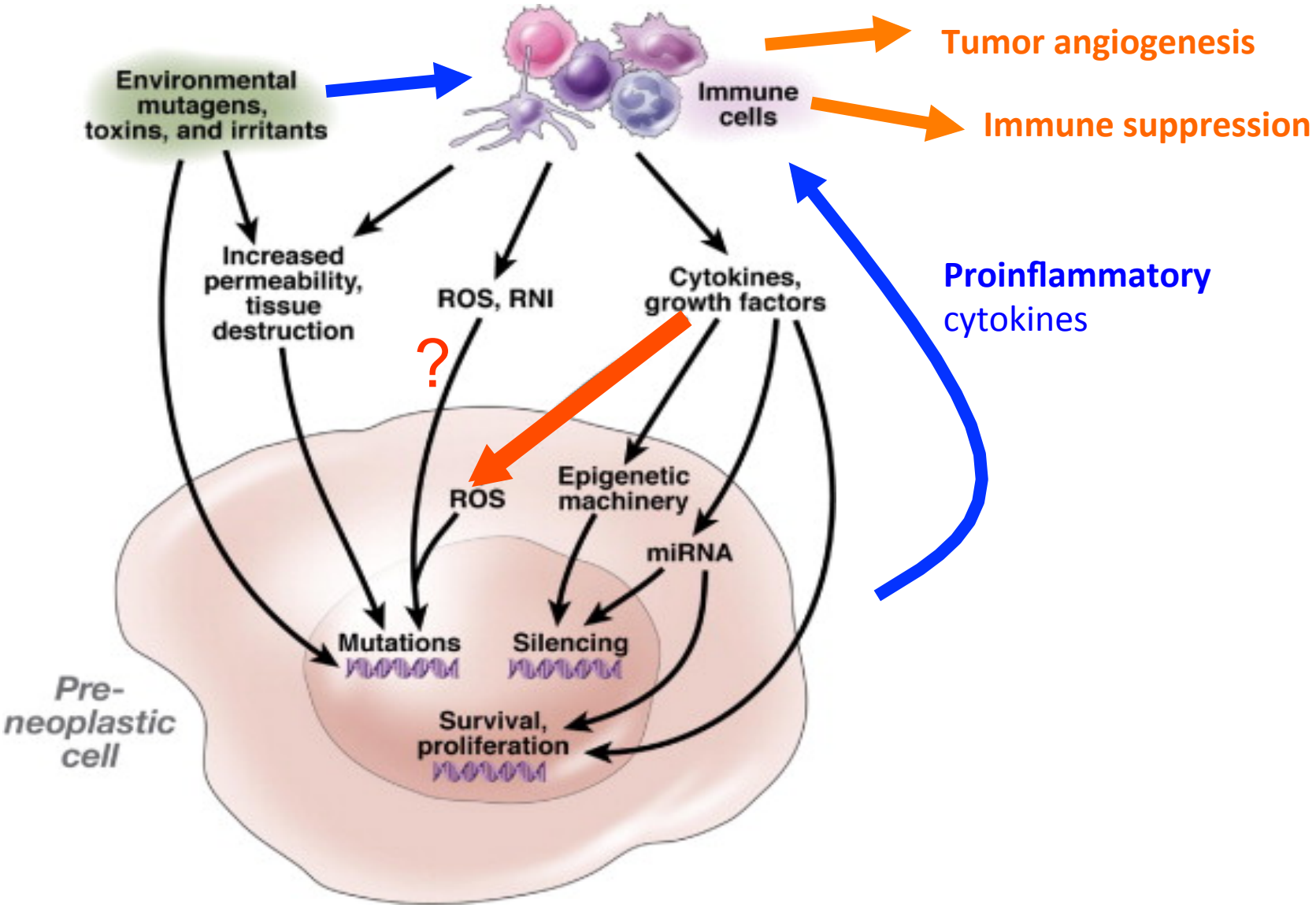
Chronic pancreatitis
Pancreatic Cancer

Inflammation, the Janus of cancer: Pro- versus anti-tumor effects



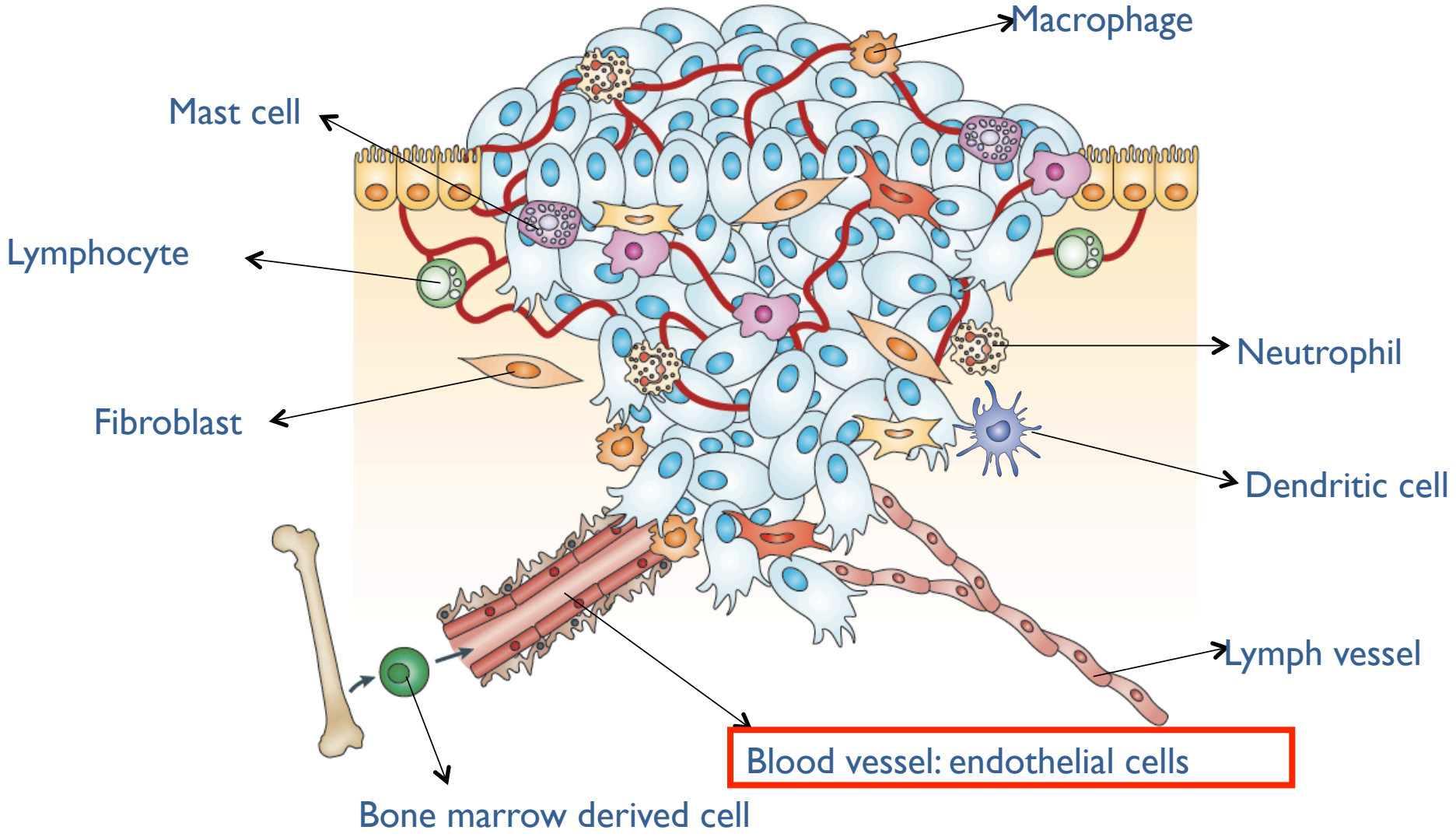
Adapted from Grivennikov et al., *Cell* 2010

Cross-talk between cancer and inflammatory cells fosters cancer-cell evolution and malignant progression



Tumor angiogenesis

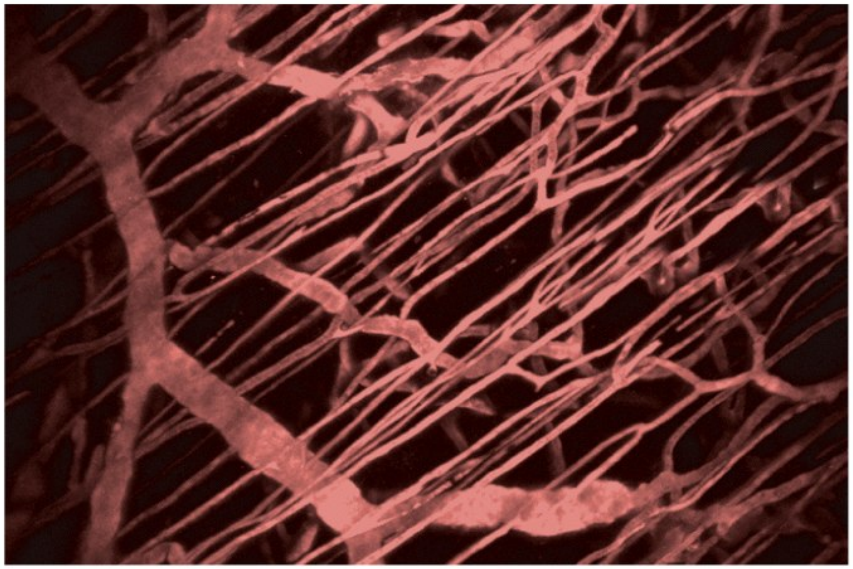
Tumor-associated stromal cells: vascular endothelial cells and angiogenesis

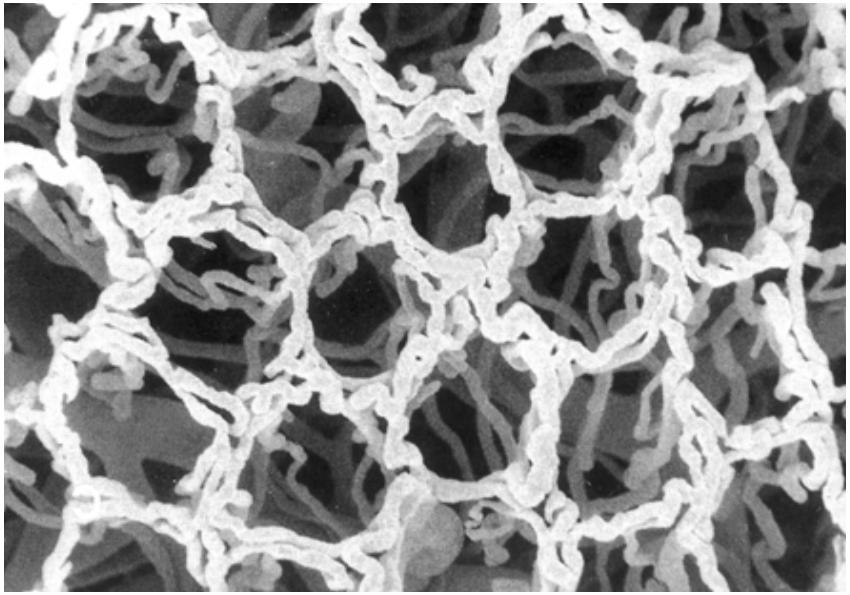


Joyce et al., *Nat. Rev. Cancer*, 2009

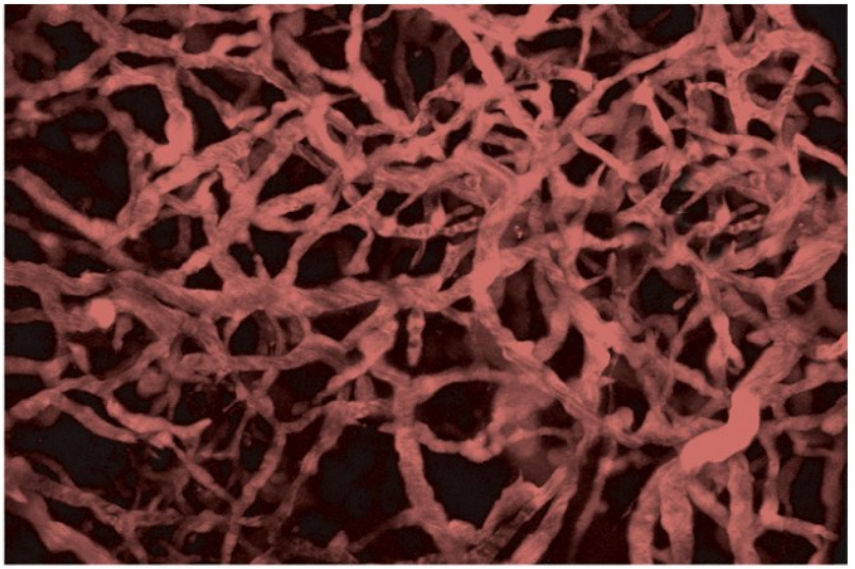
Tumor blood vessels differ from “normal” vessels

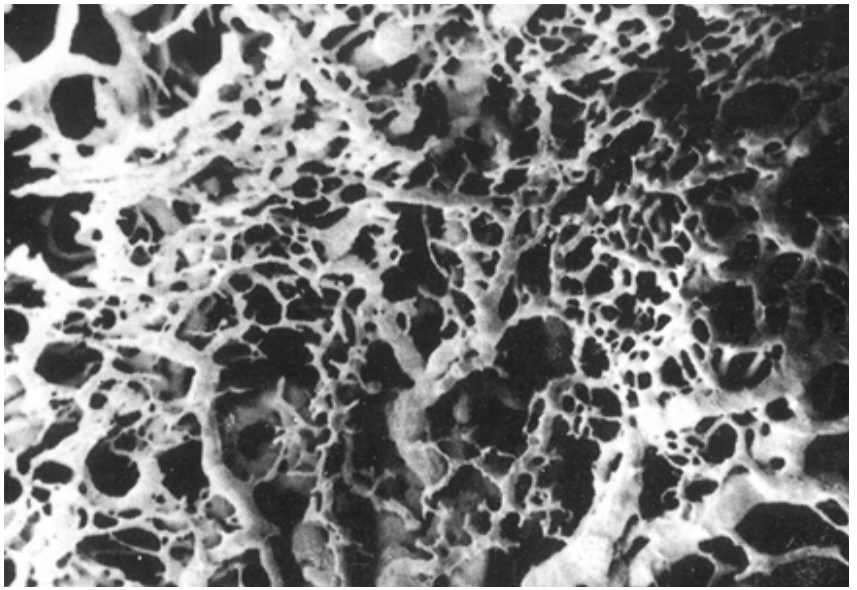
normal





cancer



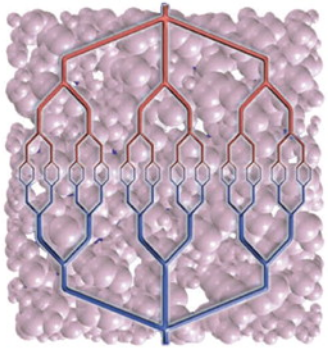


Features of tumor blood vessels

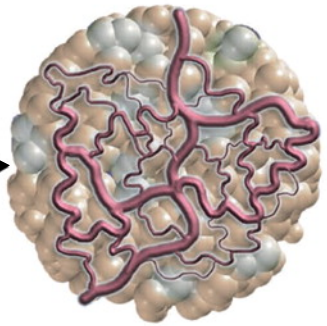
Normal

Tumor

Organization in arteries, veins and capillaries

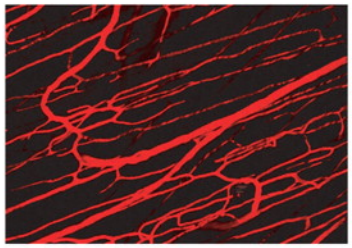


Tumor angiogenesis



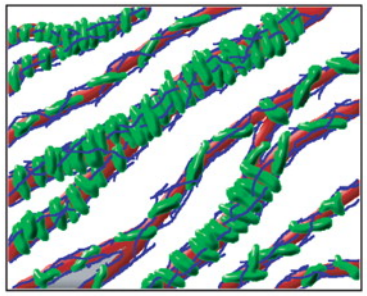
No distinct arteries and veines

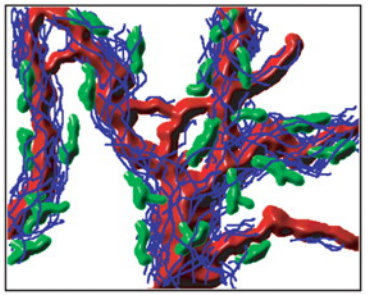
Regular morphology



Irregular morphology

High and even pericyte coverage (maturation; stability)

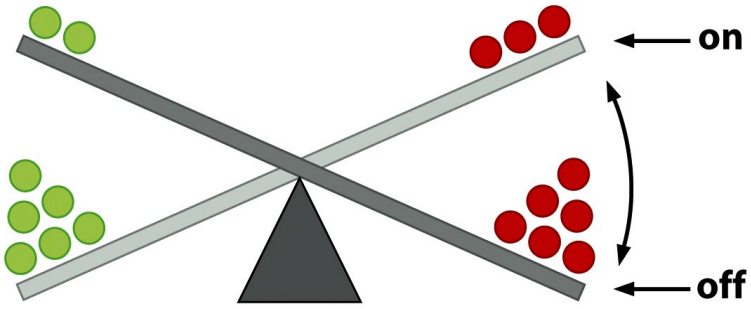




Uneven pericyte coverage (immature, unstable, leaky)

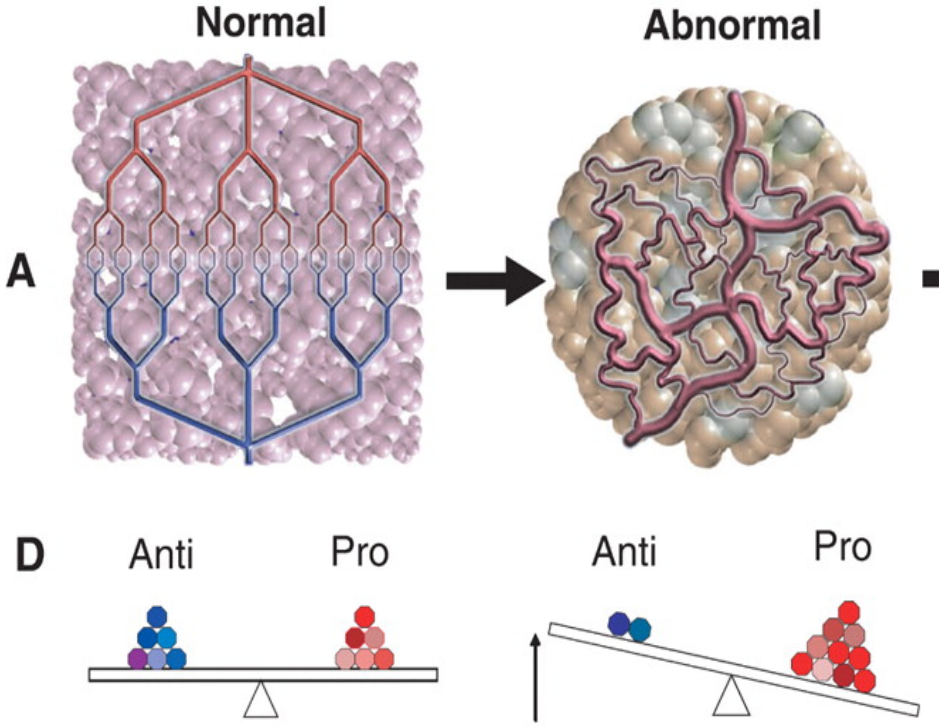
Because of these features, tumor blood vessels are poorly functional, leaky and provide **inadequate** oxygen and nutrient levels to the tumor mass

Excessive amounts of proangiogenic growth factors (over endogenous inhibitors) activate the angiogenic switch and sustain relentless tumor angiogenesis



activators
VEGF-A
VEGF-B, -C
FGF1 (aFGF)
FGF2 (bFGF)
other FGFs
ANG2

inhibitors
thrombospondin-1, -2
interferon α/β
angiostatin
endostatin
collagen IV fragments
etc.



Does tumor inflammation influence angiogenesis?