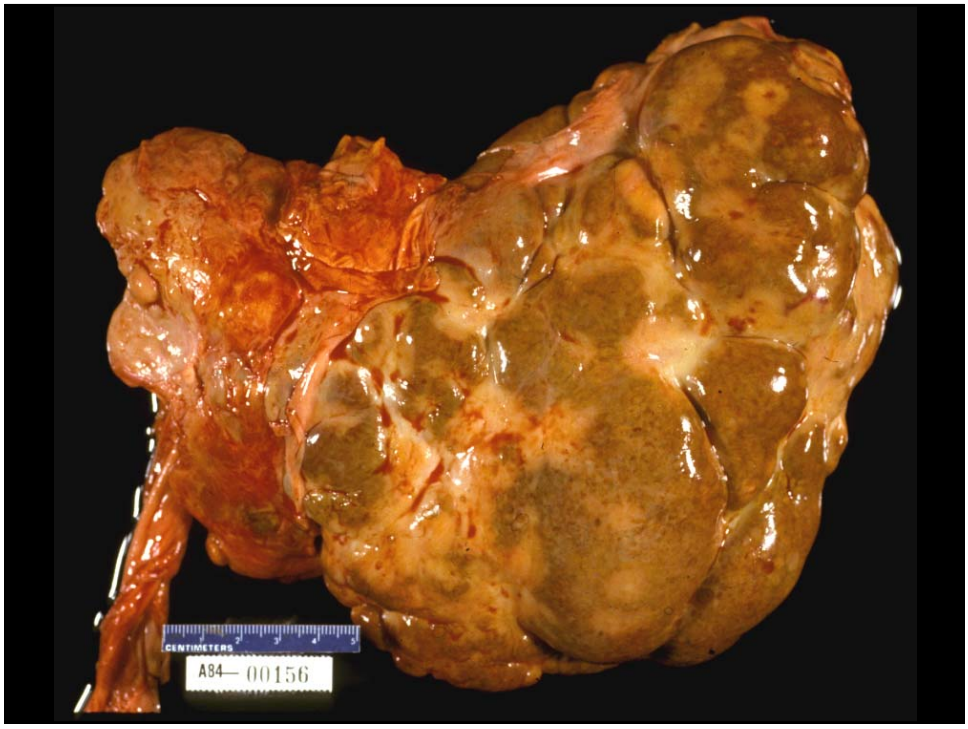


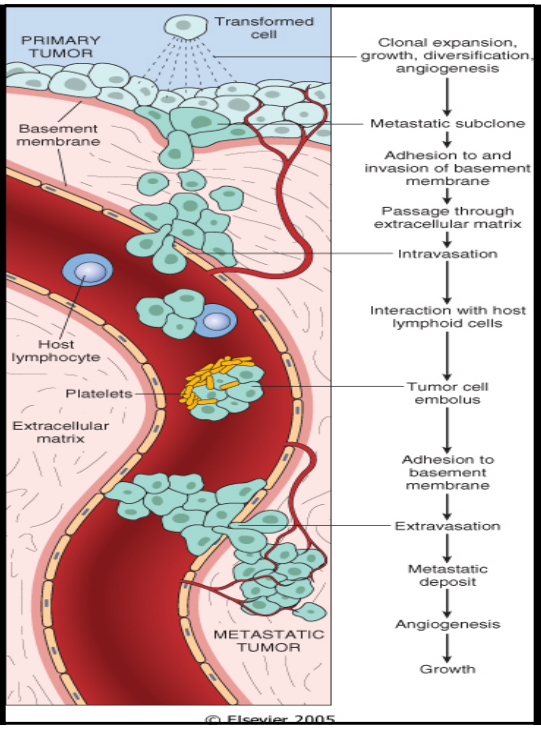
Modes of Spread

1. Lymphatic spread – colon carcinoma
2. Hematogenous spread – renal cell carcinoma

Tumor Progression to Metastasis

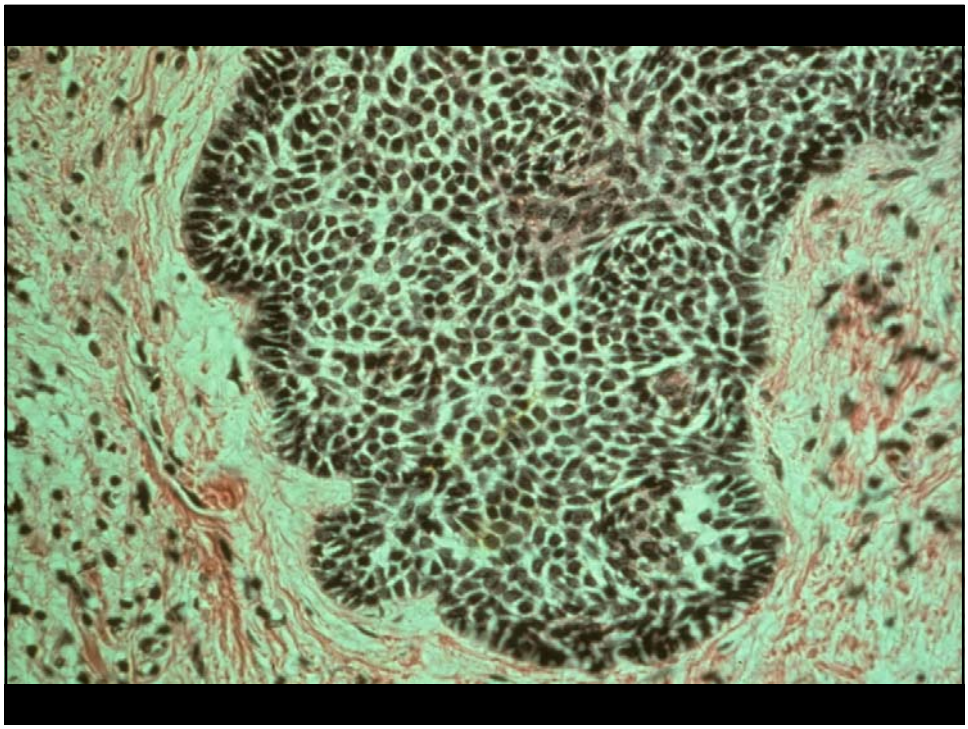
Multiple Genetic Changes Lead To:

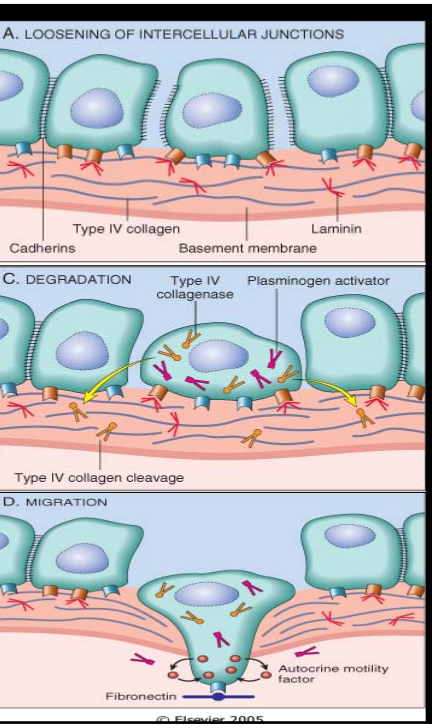
- Loss of regulated growth or death
- Invasion
- Increased angiogenesis
- Cell adhesive changes
- Metastasis

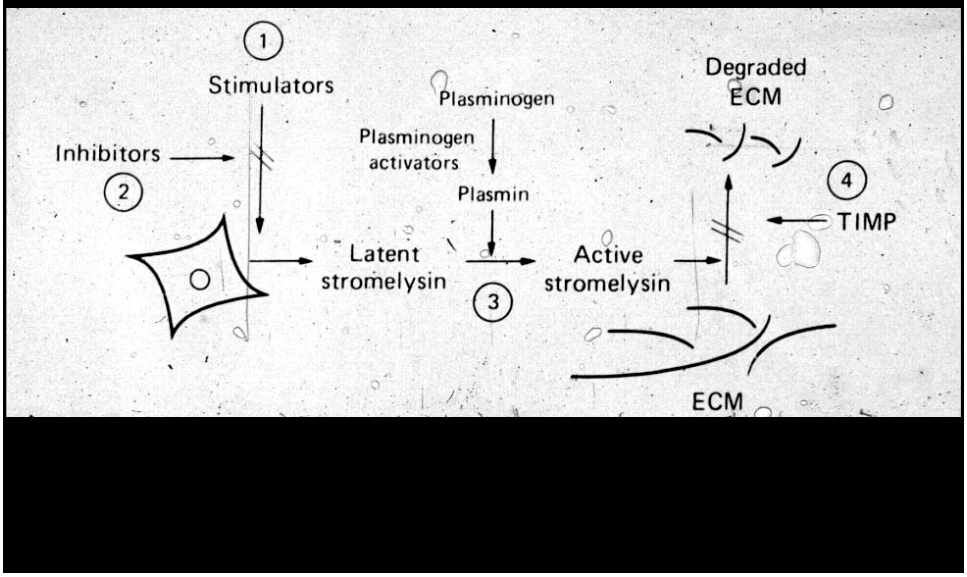


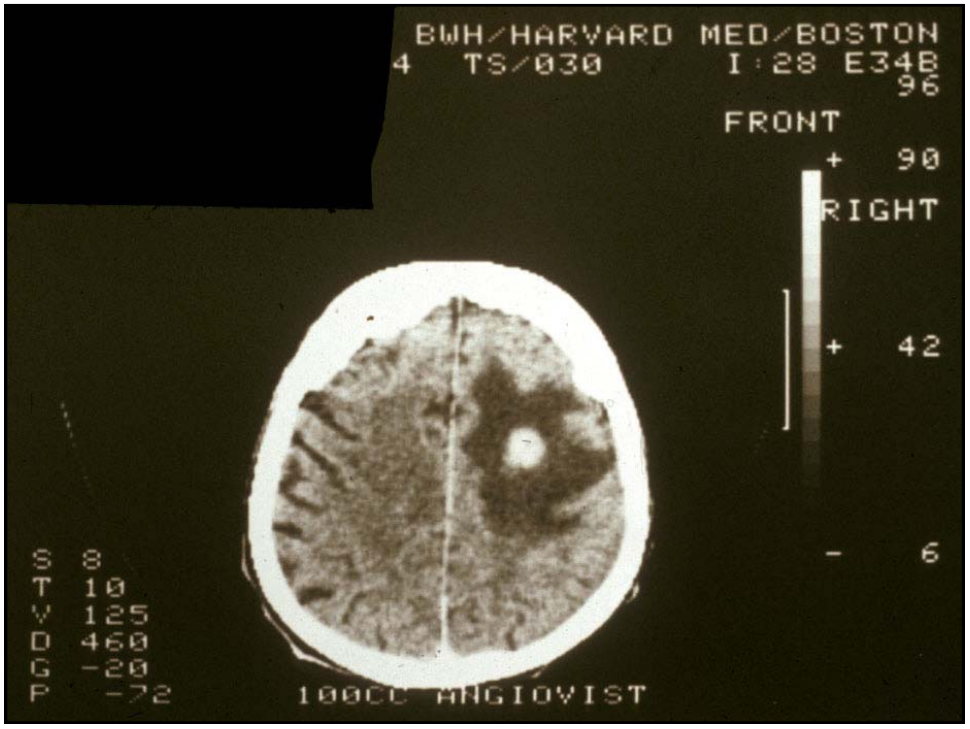
Metastasis Steps

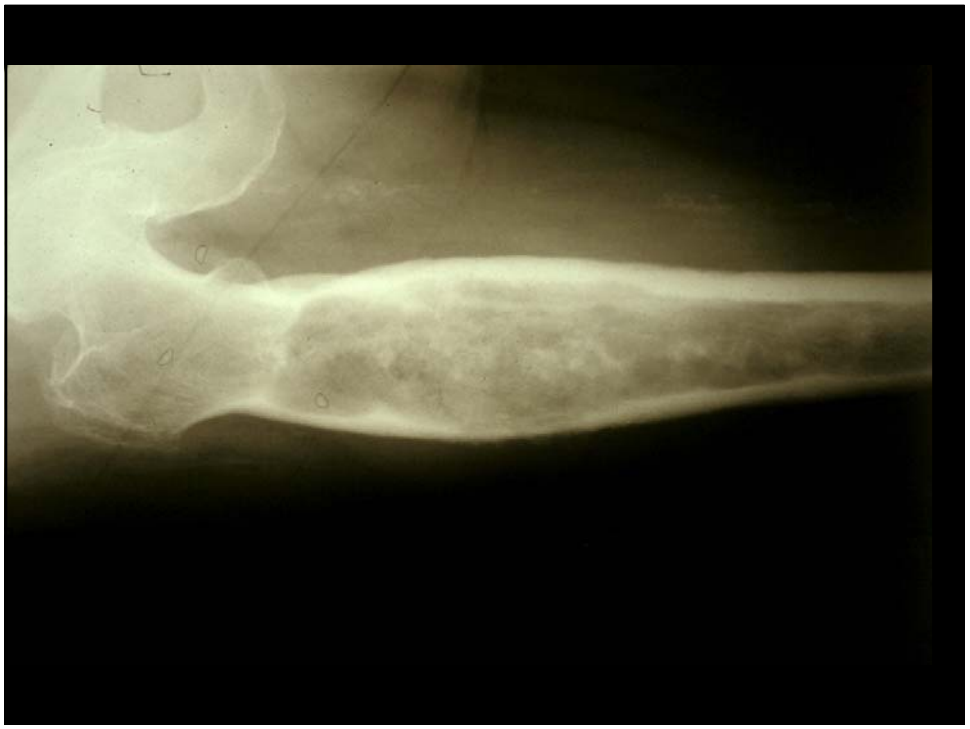
- Invasion – necessary by not sufficient
- Increased protease activity necessary to degrade basement membrane and other tissue compartments.
- Basal cell carcinoma – an example of an invasive but not metastatic tumor.

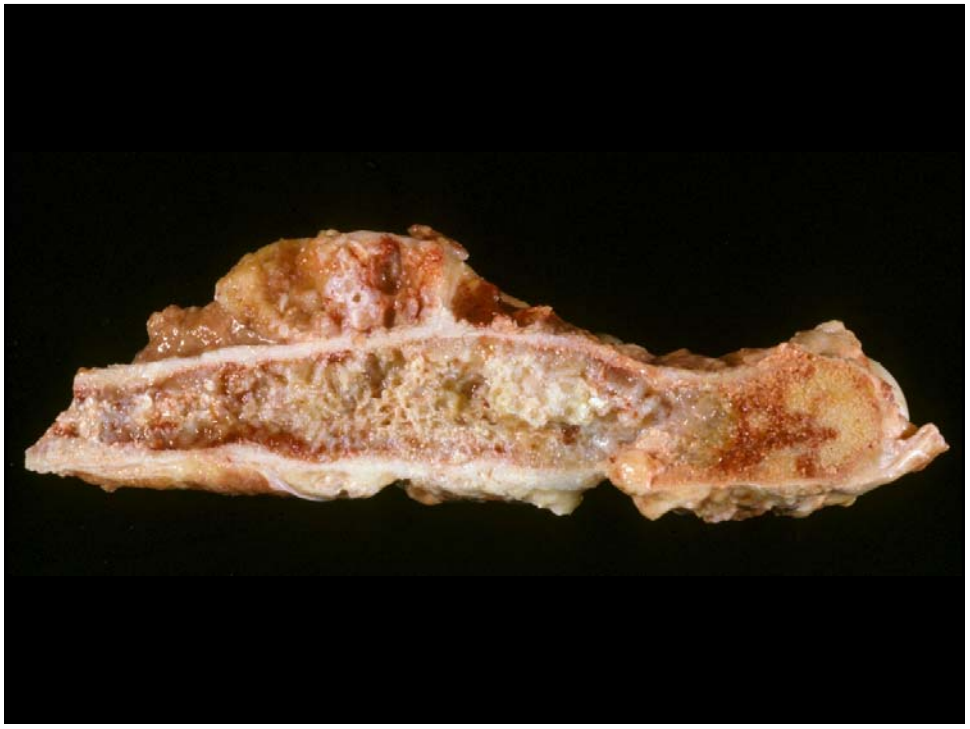


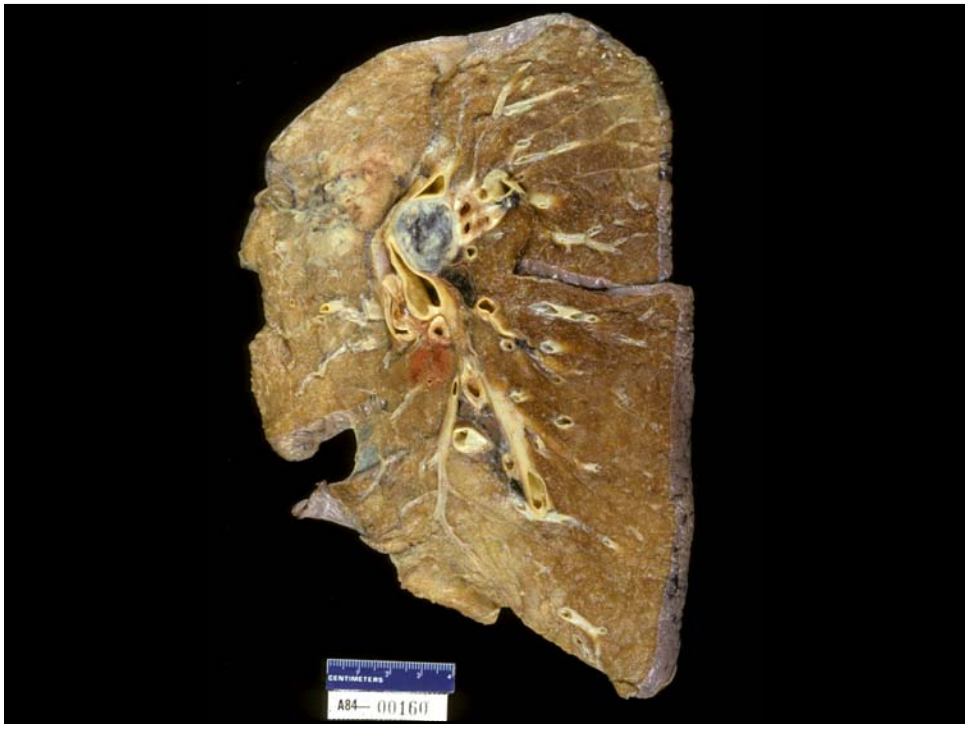

A. LOOSENING OF INTERCELLULAR JUNCTIONS
Cadherins
Type IV collagen
Basement membrane
Laminin
C. DEGRADATION
Type IV collagenase
Plasminogen activator
Type IV collagen cleavage
D. MIGRATION
Autocrine motility factor
Fibronectin

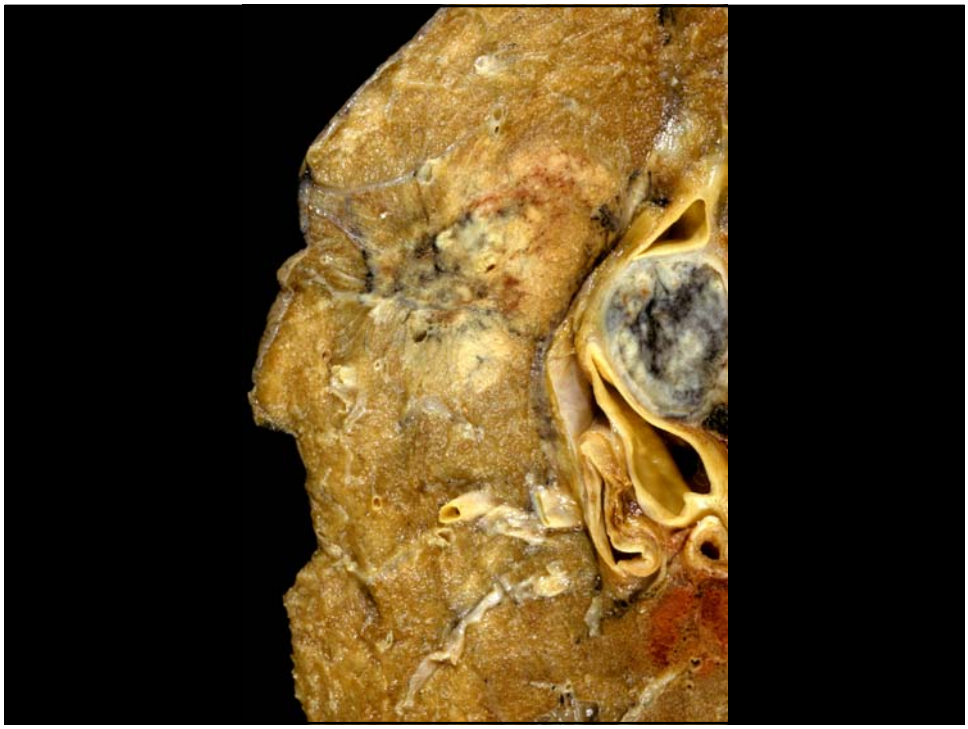

1
Stimulators
Inhibitors
2
Plasminogen
Plasminogen activators
Plasmin
Latent stromelysin
3
Active stromelysin
Degraded ECM
4
TIMP
ECM


BWH/HARVARD MED/BOSTON
4 TS/030 I:28 E34B
96
FRONT
+ 90
RIGHT
+ 42
- 6
S 8
T 10
V 125
D 460
G -20
P -72
100CC ANGIOVIST



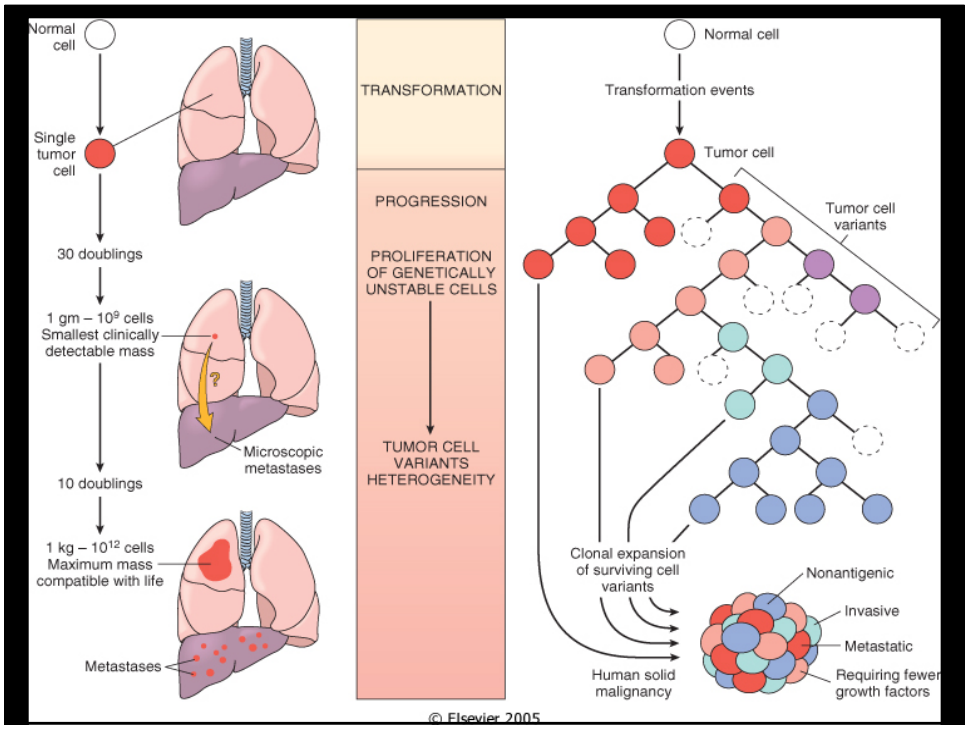



CENTIMETERS
A84— 00160



Metastasis Concepts

1. Only a small subset of tumor cells can metastasize.
2. The increased genetic instability of tumors leads to heterogeneity and the generation of metastatic variants.
3. Remember that often by the time a tumor is identified clinically there may be cells which have acquired metastatic ability



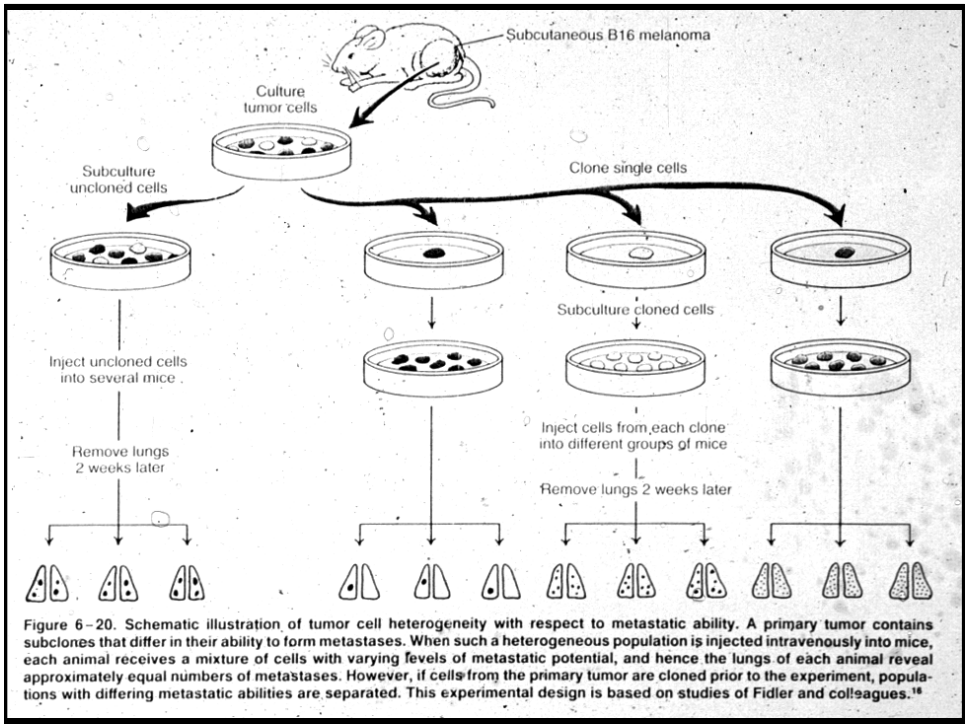


Figure 6–20. Schematic illustration of tumor cell heterogeneity with respect to metastatic ability. A primary tumor contains subclones that differ in their ability to form metastases. When such a heterogeneous population is injected intravenously into mice, each animal receives a mixture of cells with varying levels of metastatic potential, and hence the lungs of each animal reveal approximately equal numbers of metastases. However, if cells from the primary tumor are cloned prior to the experiment, populations with differing metastatic abilities are separated. This experimental design is based on studies of Fidler and colleagues.[16]

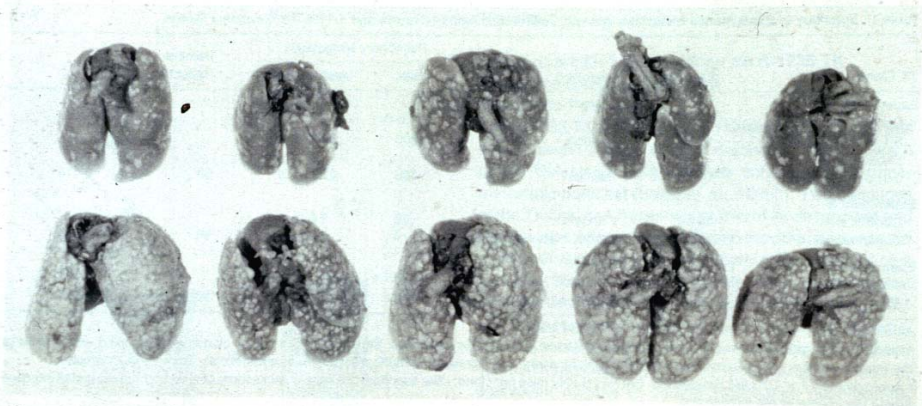
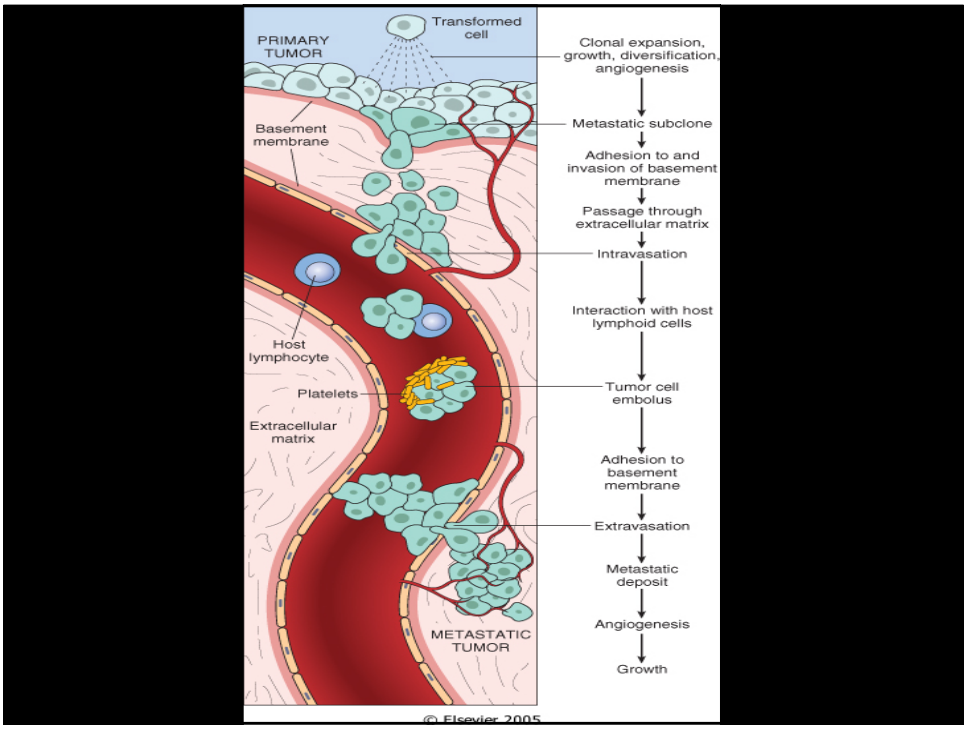


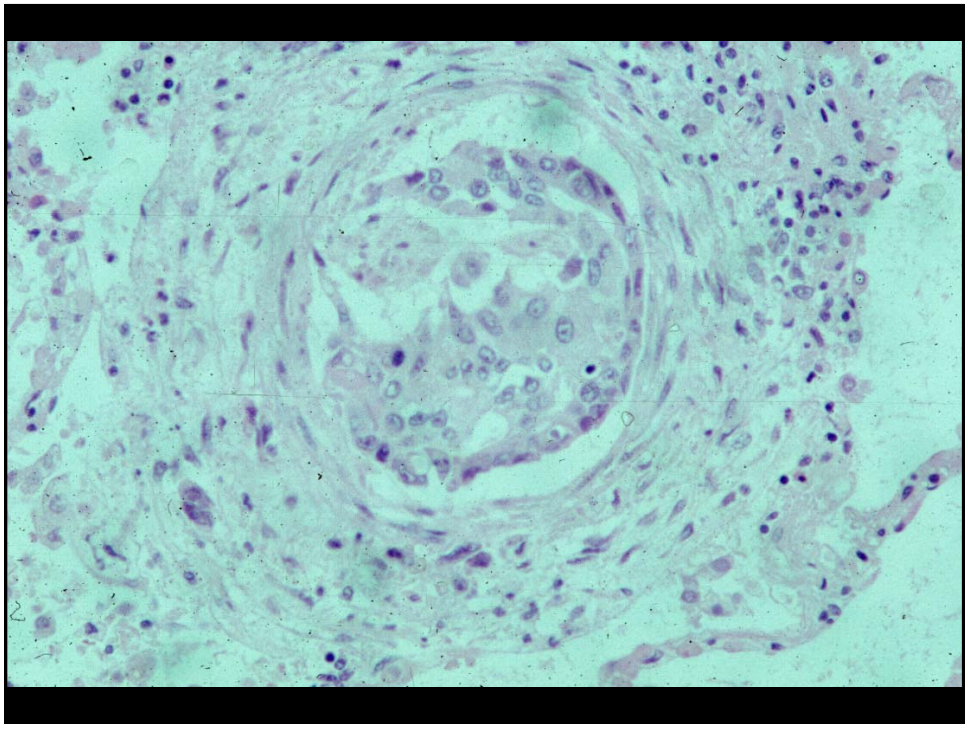
Figure 2. Experimental Metastatic Potential of *nm23–1*⁺ A3 Cells and Control-Transfected A2 Cells

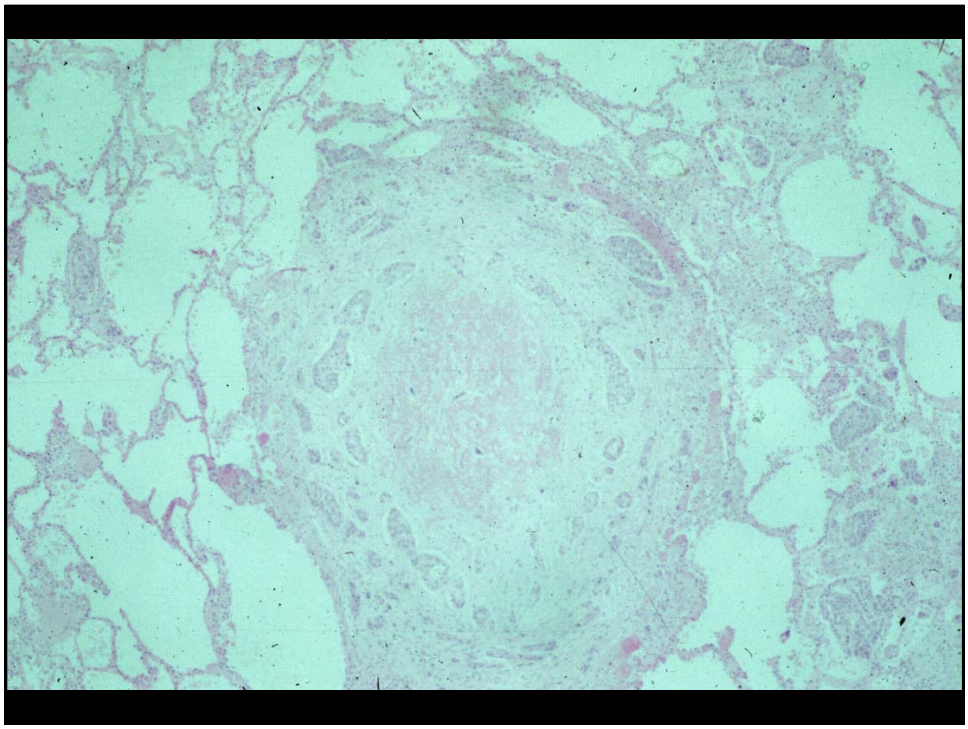
Approximately 1 × 10^5 cells from each clone were injected intravenously into the tail veins of five NIH Nu/Nu mice. Mice were sacrificed 3 weeks postinjection and the lungs preserved in Bouin's solution. The top row shows *nm23–1*⁺ A3 cells, and the bottom row shows control-transfected A2 cells.

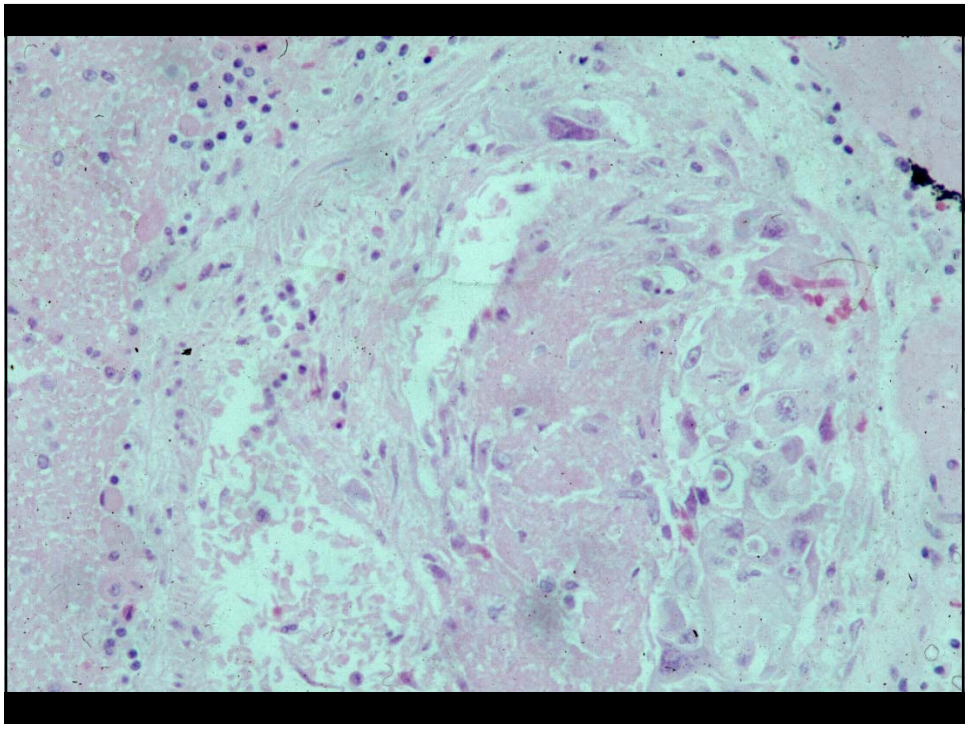
Metastasis Steps

- After the cells enter the circulation (or lymphatics) they must be able to survive.
- One mechanism is platelet-tumor emboli.
- Another is lack of immune recognition.



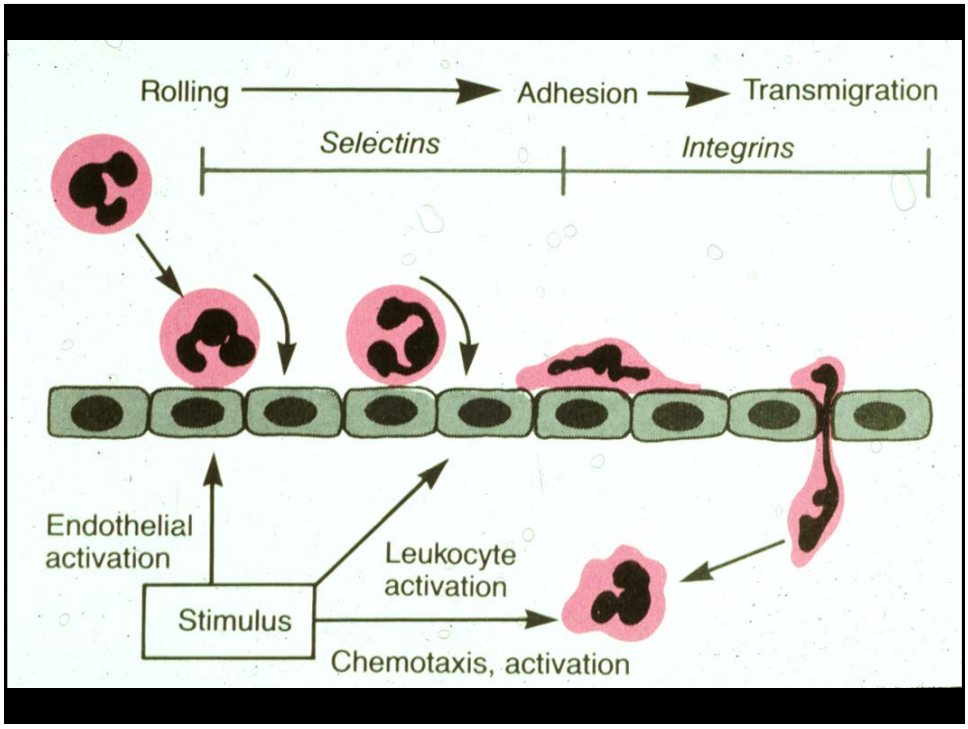


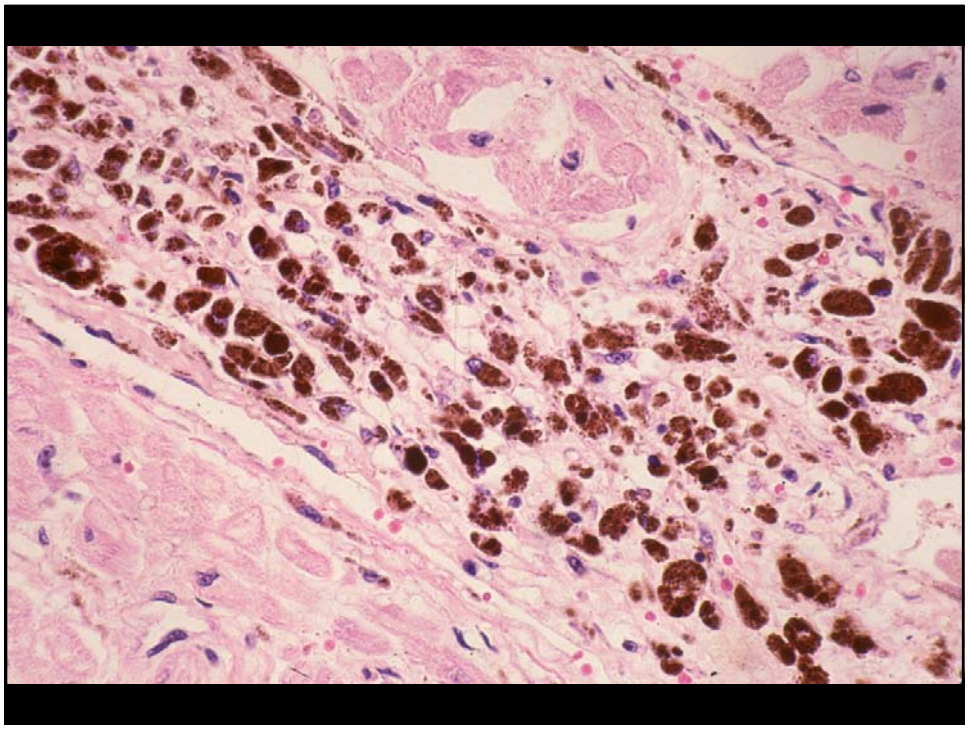




Metastasis Steps

- Efficient metastatic spread requires cells to cross endothelium and basement membranes to reach tissues.
- Melanoma – a very deadly tumor, mimicks lymphocytes and monocytes in crossing endothelium.
- These tumor cells have $\alpha 4\beta 1$ integrin and make interleukins to activate endothelium to express VCAM.

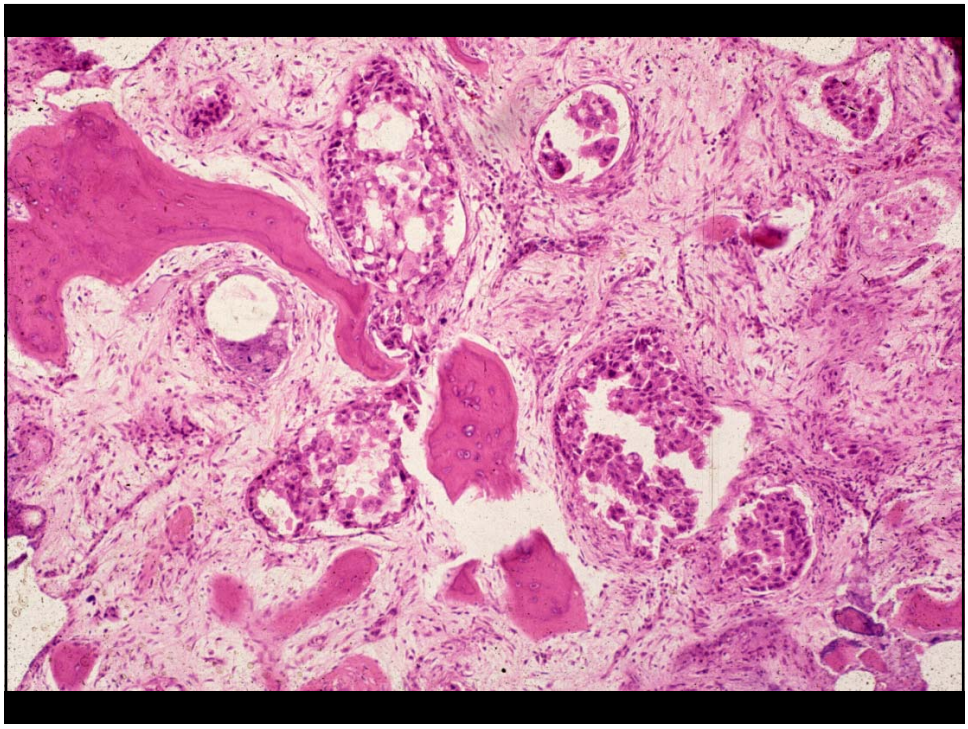

Rolling
Adhesion
Transmigration
Selectins
Integrins
Endothelial activation
Leukocyte activation
Stimulus
Chemotaxis, activation

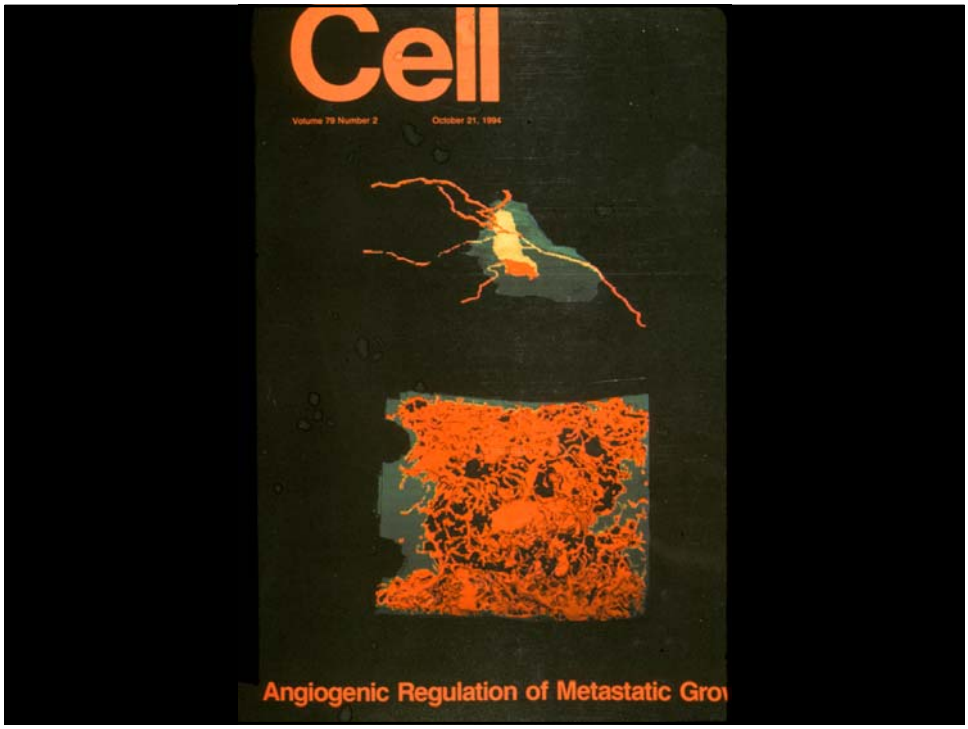


Metastasis Steps

Why do some tumors prefer selected tissues?

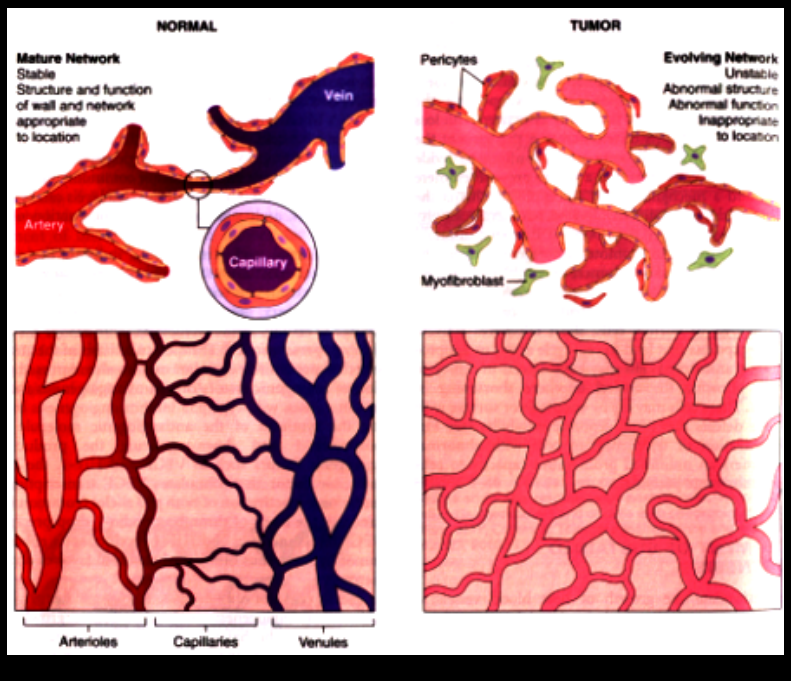
- Accessibility due to differences in tissue endothelium
- Enhanced growth or survival in specific tissues, due to growth factors or extracellular matrix.
- A striking example is bone growth in breast and prostate cancers.




Cell
Volume 79 Number 2
October 21, 1994
Angiogenic Regulation of Metastatic Gro

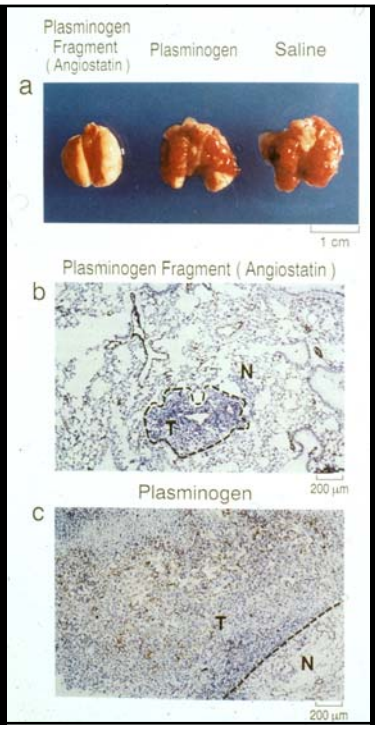
Angiogenesis and Metastasis

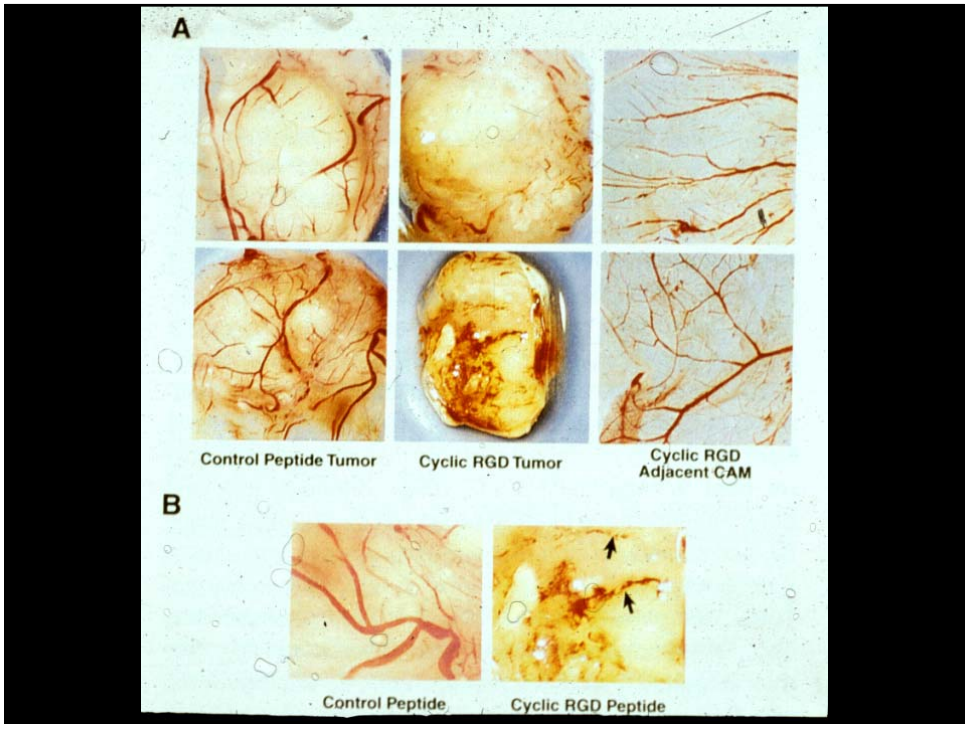
- Highly metastatic tumors may produce angiogenic stimuli, such as fibroblast growth factor (FGF).
- Non-metastatic tumors may produce inhibitors of angiogenesis (angiostatins).
- Blockade of tumor angiogenesis may shrink metastases

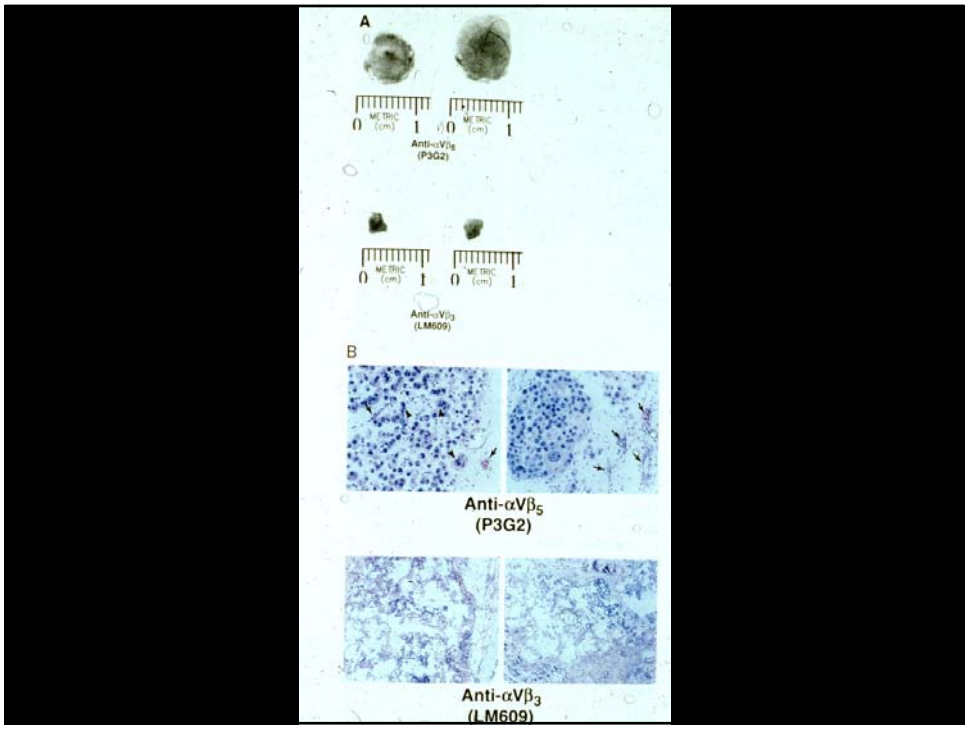


Tumor Angiogenesis and the Magic Bullet

- Blockade of endothelial integrins (particularly $\alpha v\beta 3$) may prevent tumor neovascularization.
- This integrin is expressed on activated, migrating endothelium, but not resting.
- Anti-$\alpha v\beta 3$ peptides cause tumor associated endothelium to die, leading to necrosis of tumors.




A
Control Peptide Tumor
Cyclic RGD Tumor
Cyclic RGD
Adjacent CAM
B
Control Peptide
Cyclic RGD Peptide


A
Anti-αVβ5
(P3G2)
Anti-αVβ3
(LM609)
B
Anti-αVβ5
(P3G2)
Anti-αVβ3
(LM609)

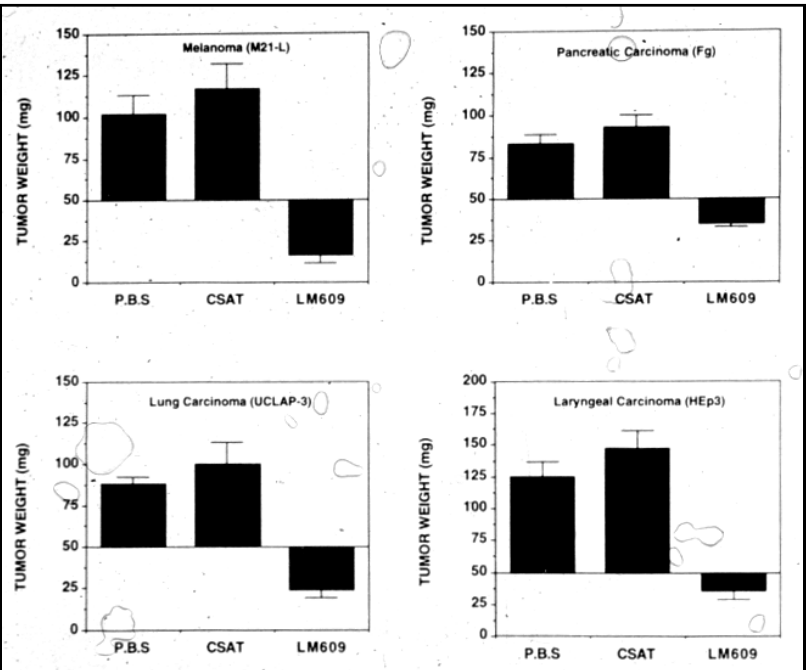
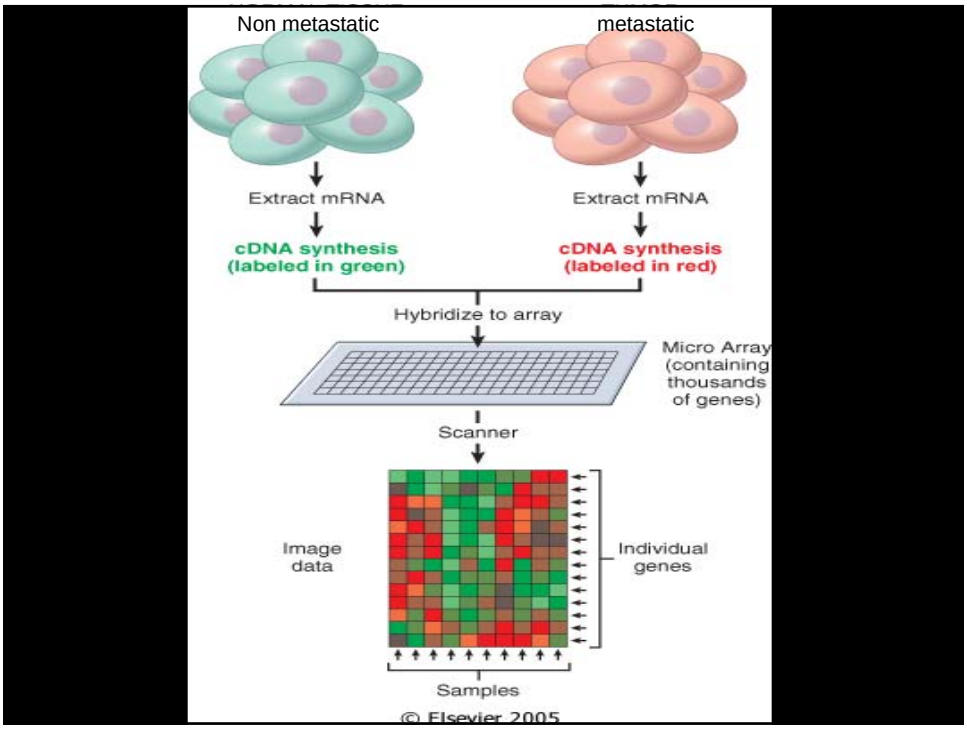
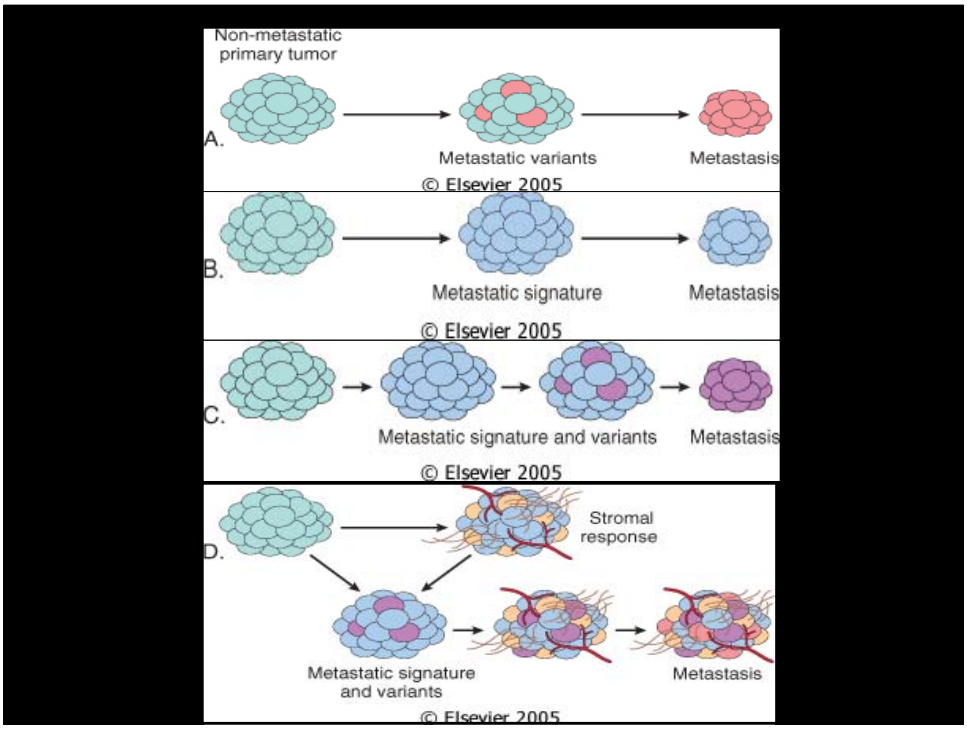


Figure 2. Inhibition of Tumor Growth by Antagonists of $\alpha_v\beta_3$ Integrin

Metastasis Genes

- Despite years of searching, there is no one gene or even a common small subset of genes that lead to metastasis.
- However, for some tumors, there appears to be a metastasis signature, a group of genes whose expression correlates with metastasis.
- This signature appears to be the result of a number of activated signaling pathways, rather then a single one that could be inhibited.

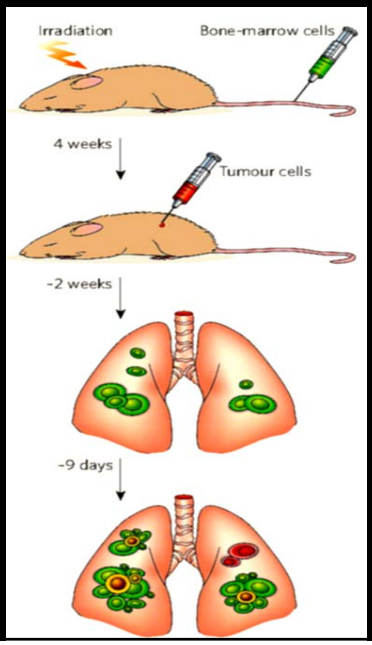

Non metastatic
metastatic
Extract mRNA
Extract mRNA
cDNA synthesis (labeled in green)
cDNA synthesis (labeled in red)
Hybridize to array
Micro Array (containing thousands of genes)
Scanner
Image data
Individual genes
Samples
© Elsevier 2005


Non-metastatic primary tumor
A.
Metastatic variants
Metastasis
© Elsevier 2005
B.
Metastatic signature
Metastasis
© Elsevier 2005
C.
Metastatic signature and variants
Metastasis
© Elsevier 2005
D.
Stromal response
Metastatic signature and variants
Metastasis
© Elsevier 2005

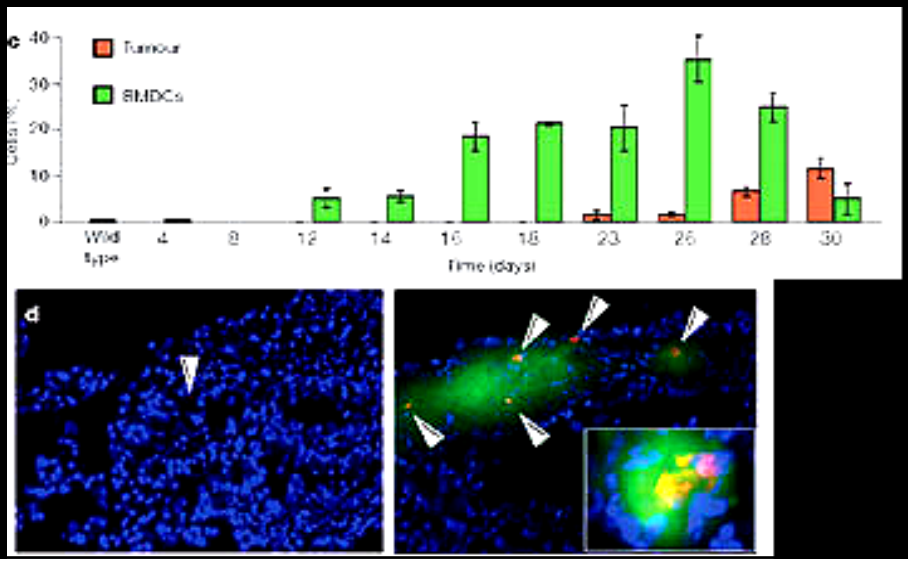
Regulators of Metastasis

1. Many genetics screens have been used to identify metastasis suppressors or required genes.
2. These screens have evolved as the technologies have changed, but the result is usually the same.
3. There is not one key regulator or master switch which turns on the metastatic program.
4. For many carcinomas, activation of RTK's such as EGFR, HER2 or Met may be a critical regulator of such a program.

Is there a pre-metastatic niche?



Is there a pre-metastatic niche? Yes, in experimental metastasis



The production of the "pre-metastatic" niche

1. Lyden and colleagues have shown that bone marrow derived cells (BMDC) precede tumor cells at future metastatic sites.

2. The BMDC are VEGFR1 positive cells. Removing these cells from the marrow prevents experimental metastasis. Unknown factors secreted by the tumor cells stimulate these BMDC to go to distant sites.

3. The more highly metastatic cell lines (such as melanoma) were much better at stimulation of BMDCs than less metastatic ones.

4. This result may have future implications if it is true for human tumors.

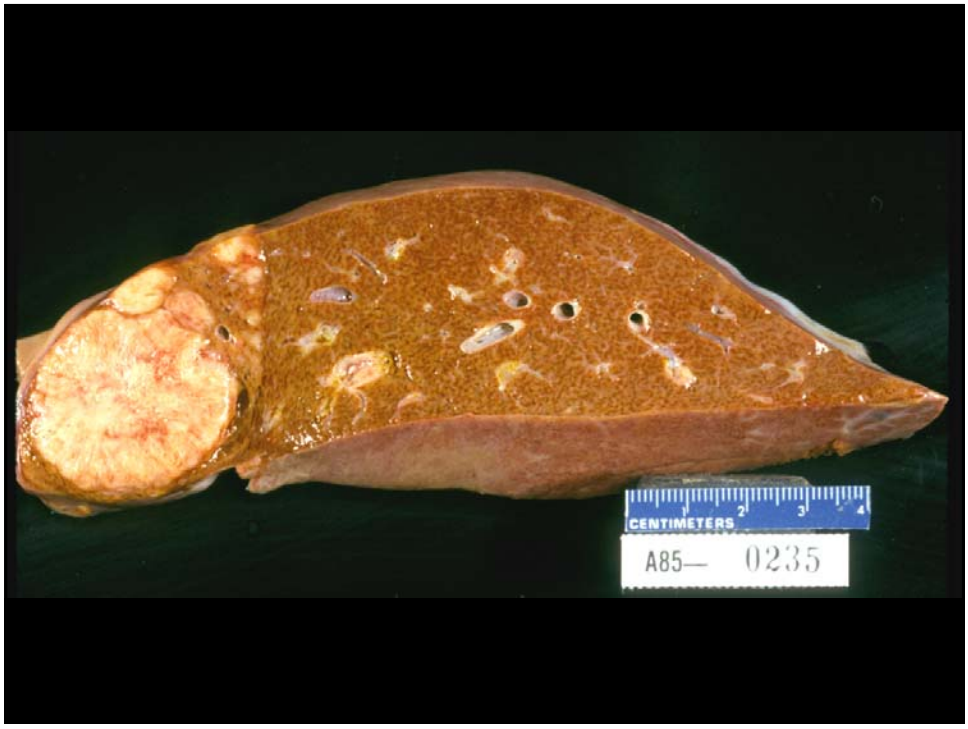


Table 7–10. INTERMEDIATE FILAMENTS AND THEIR DISTRIBUTION

Keratins	Carcinomas Mesothelioma
Desmin	Muscle tumors: smooth, striated
Vimentin	Mesenchymal tumors, some carcinomas
Glial filaments	Gliomatous tumors
Neurofilaments	Neuronal tumors

Table 7–11. SELECTED TUMOR MARKERS

MARKERS	ASSOCIATED CANCERS
Hormones	
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	See Paraneoplastic Syndromes in Table 7–9
Oncofetal Antigens	
Alpha-fetoprotein	Liver cell cancer, nonseminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and breast
Isoenzymes	
Prostatic acid phosphatase	Prostate cancer
Neuron-specific enolase	Small cell cancer of lung, neuroblastoma
Specific Proteins	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen	Prostate cancer
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer

based amplification of *bcr-abl* transcripts. The expression of the MyoD1 gene is restricted to cells of

test to support the diagnosis. Some are also of value in determining