Metastasis

1. The metastatic cascade

2. Pathologic features of metastasis

3. Therapeutic ramifications
Sir James Paget (1814-1899)

British Surgeon/Pathologist

Paget’s disease of bone

Paget’s disease of the nipple (intraductal Ca breast spreading to skin of nipple)
Stephen Paget, MD
(1855-1926)

METASTASIS:
“Seed and Soil”


“the best work in pathology of cancer is done by those who...are studying the nature of the seed...”...

“the observations of the properties of the soil may also be useful.”
liver

Carcinoma of breast
Which malignant cells will metastasize?

1. **Subclone theory**
   - A specific clone has the prop’s for metastasis

2. **Cancer stem cell theory**
   - Only the stem cells have the prop’s for metastasis

3. **Genetic signature theory**
   - Many malignant cells at different stages have the signature genes allowing metastasis

- 70-gene signature for mets in breast Ca
epithelium

B.M.: laminin + coll. IV

ECM

blood vessels: cap./venule/lymphatic

distant sites

lungs

distant sites

bone

brain

lymph nodes

liver
1. Invasion of B.M. & ECM

- B.M.: laminin + coll. IV
- ECM

2. Intravasation & vasc. dissemination
- blood vessels: cap./venule/lymphatic

3. Extravasation, colonization & growth
- TUM: lungs, bone, brain, lymph nodes, liver, distant sites
Stage 1: Invasion of B.M. and ECM

1. Loosening of tumor cells

- Mutation of E-cadherin
- Inappropriate expression of SNAIL & TWIST
  (which regulate E-cadh. expres.)

(Secondary effect: E-cadherin normally sequesters β-catenin—cell proliferator—so with less sequestered, more tumor cells proliferate)
2. Degradation of B.M. & ECM

- MMP’s
  - (esp. MMP9: gelatinase action on b.m. type IV collagen)
- Cathepsin D
- Urokinase plasminogen activator
- Type IV collagenase

blood vessels: cap./venule/lymphatic
integrin with affinity for laminin and other ECM proteins

3. Change in attachment of tumor cells to ECM proteins
4. Locomotion of tumor cells
Stage 2: Intravasation & vasc. dissemination

HOSTILE ENVIRONMENT:
Most tumor cells do not survive

TUM
B.M.: laminin + coll. IV

epithelium

ECM

platelet-tumor emboli

Up-regulate adh. molecules for endothel.

NK cell

mac

Vessel size
Shear stress

TNF-α
IFN-γ
Stage 3: Extravasation, colonization & growth

- Angiogenesis
- EMT
- Chemokine express.
- Adhesion molecules
- Down-regulate
  “metastasis suppressor proteins”

blood vessels: cap./venule/lymphatic
Alveolar space

Example: METASTASIS TO LUNG
Example: METASTASIS TO LUNG
Angiopoietins 1 & 2

- Ang-1
- TIE-2 receptor
- pericyte
- VEGFR

HIF-1α (hypoxia inducible factor)

- TGF-α, β
- PDGF
- FGF
- EGF
- angiogenin

VEGF

A, B, C, D, E:
- angiogenesis
- endothelial mitosis

lymphangiogenesis
Anti-angiogenic factors

• thrombospondin-1

• p53 expression
  \( \rightarrow \) VEGF expression

• Proteases (from tumor cells or from stromal cells):
  \textit{proteolytic cleavage}:
  
  Plasminogen \( \rightarrow \) angiostatin
  Collagen \( \rightarrow \) endostain
  Transthyretin \( \rightarrow \) vasculostatin
liver

Carcinoma of breast
Chemokine receptors on tumor Cells: ligands in metastatic sites

N Engl J Med
2001; 345: 833-835
Breast Carcinoma (invasive)
intraductal carcinoma

fibrosis (desmoplasia)

necrosis

invasive Ca

lymphatic

Breast Carcinoma (intraductal and invasive)
Ductal carcinoma
In situ (DCIS)
invasion

B.M.
Intraductal and invasive Carcinoma
Blood vessels

Inflammation

Ingrowth of fibroblasts & stroma
General Modes of Metastasis

carcinoma → lymphatics → regional lymph nodes

sarcoma → veins → lungs → bone
Common Sites of Metastasis

- Colorectal
- Breast
- Renal cell Ca
- Hepatocellular Ca

Lung

- Colorectal
- Pancreas
- Other GI: carcinoid, bile ducts
- Lung
- Breast

Liver
Common Sites of Metastasis

- Breast
- Prostate
- Renal cell Ca

Bone

- Lung
- Breast
- Melanoma
- Renal cell Ca

Brain

Neuroaxis

Vert. veins
Unique Sites of Metastasis

- Virchow’s node (supraclavicular node)
- Gastric Ca (signet ring Ca)
- Krukenberg tumor (bilateral ovarian mets)
Lung Carcinoma metastasis to Adrenal

Source: University of Alberta, Dep’t of Laboratory Medicine & Pathology
Therapeutic Implications
TUM lungs bone brain epithelium
B.M.: laminin + coll. IV liver
ECM lymph nodes
distant sites
blood vessels: cap./venule/lymphatic
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mech. of action</th>
<th>Neoplasm(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Monoclonal Ab against VEGF</td>
<td>colorectal</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multi-kinase inhibitor of VEGFR, PDGFR</td>
<td>renal cell; GIST</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multi-kinase inhibitor: VEGFR, PDGFR, C-kit, Raf</td>
<td>renal cell</td>
</tr>
</tbody>
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**Anti-angiogenic agents**

**Anti-chemokine receptors**